An investigation into Theory of Mind abilities in individuals at enhanced risk of schizophrenia

Dominic Keigwin Simon Marjoram BSc (Hons).

Contents

List of Tables

List of Figures

It is the Mind
that is the mind
confusing the mind.
Do not leave the mind,
O mind,
to the mind.

Japanese poem taken from "The book of family traditions on the art of war". Jagyu Munemori, 1632.

Acknowledgements

I would like to offer my thanks to my principal supervisor, Dr Stephen Lawrie, for his continued support and guidance throughout the course of this thesis. I would also like to offer special thanks to my second supervisor, Professor Eve Johnstone, for her advice and support and also for allowing me to work on the Edinburgh High Risk Study (EHRS). Special thanks are due to Dr's Whalley, Job, McIntosh, Miller, and Siminotto for sharing their advice, expertise and time. Special thanks also go out to all EHRS participants and their families and the patient and control volunteers from the pilot study, whose kindly volunteered time made this thesis possible.

The EHRS was funded by a MRC programme grant. Scanning was conducted at the Brain Imaging Research Centre (BIRC) for Scotland at the Western General Hospital, Edinburgh. BIRC is funded by the Scottish Higher Education Funding Council (SHEFC).

I would like to also thank the staff at the Western General Hospital, particularly Professor Joanna Wardlaw, Dr Ian Marshall and the radiographers.

Finally, I would like to thank the MRC for funding my PhD.

Declaration

My role in the EHRS was to collect and document both neuropsychological and functional imaging data, and to analyse and interpret these data accordingly.

The collection of the data reported in this thesis began in June 2003 and was completed in February 2005. A research assistant, Caroline Brett, recruited the first 5 EHRS participants of this thesis study and trained me in the administration of the non Theory of Mind neuropsychological tests. I recruited and tested all subsequent EHRS participants. For the Pilot study, I was assisted in the recruitment and testing of the control participants by Howard Tansley, a medical student.

For the analysis of the Theory of Mind and self-monitoring neuropsychological tasks, advice on statistical analysis was given by Dr Patrick Miller and Dr Andrew McIntosh.

The analysis of the functional imaging data was conducted by myself under the supervision of Dr Heather Whalley and Dr Dominic Job. I was responsible for reporting and interpreting the results.

I was the primary author on the four research papers.

This work has not been submitted for any other degree or professional qualification. I declare that this thesis is my own work, and the contribution to this thesis of others is clearly documented here and throughout the thesis where relevant.

Dated: 11/08/06

Abbreviations

Abbreviation	Meaning	Definition
ANOVA	Analysis of Variance	A collection of statistical models and their associated procedures which compare means by splitting the overall observed variance into different parts.
BA	Brodmann Area (1)	Cytoarchitectonically defined anatomical areas of the brain.
BADS	Behavioural Assessment of the Dysexecutive Syndrome (2)	A test battery which assesses the 'everyday' difficulties associated with the dysexecutive syndrome.
BOLD	Blood oxygen level dependent	Endogenous contrast used in fMRI based on paramagnetic properties of oxygenated and deoxygentated blood.
BPRS	The Brief Psychiatric Rating Scale (3)	Short scale for rating recent psychiatric symptoms.
BPVS	Binois and Pichot vocabulary scale (4)	French measure of verbal IQ.
CAPE	Community Assessment of Psychic Experience	Self report questionnaire on psychic experience.
CBF	Cerebral blood flow	Parameter related to cerebral haemodynamics.
CBT	Cognitive Behavioural Therapy	A form of psychotherapy using imagery, self-instruction, and related techniques to alter distorted attitudes and perceptions.
COMT	Catechol-O-Methyltransferase	An enzyme with a pivotal role in the extracellular degradation of dopamine.
CBV	Cerebral Blood Volume	Parameter related to cerebral haemodynamics.
CPT	Continuous Performance Test	A Task that measures attentions and sustained concentration abilities.
DSM IV	Diagnostic and Statistical Manual of the American Psychiatric Association (1994)	One of the two major classification manuals in psychiatry, see ICD-10.

EEG	Electroencepahalogram	Electrophysiological method for functional brain mapping based on recording transient electrical signals generated by neuronal depolarisation.
EHRS	Edinburgh High Risk Study	Longitudinal study of individuals with first and second degree relatives with schizophrenia from Scottish families. Participants are said to be of enhanced risk.
EPI	Echo Planar Imaging	Fast imaging technique used in fMRI.
fMRI	Functional Magnetic Resonance Imaging	Functional imaging technique measuring changes in blood oxygenation, based on differing magnetic properties of oxygenated and deoxygenated blood.
FOV	Field of View	Region of physical space to which the data corresponds.
FWHM	Full Width Half Maximum	Method for characterising the width of a peak on a graph. Commonly used to describe smoothing filter applied to neuroimaging data.
ICD-10	International Classification of Diseases (World Health Organisation 1993)	One of the two major classification manuals in psychiatry, see DSM IV.
MEG	Magnetoencepahalography	Electrophysiological method for functional brain mapping based on recording transient magnetic signals generated by neuronal depolarisation.
MRI	Magnetic Resonance Imaging	Imaging technique based on observing changes in the behaviour of protons in the presence of a magnetic field.
MWT	'Mehrfachwahlwortschtztest' Multiple Choice Verbal Comprehension Test (5)	German Verbal comprehension test that is similar to the 'Spot-the-Word' test.
NART	National Adult Reading Test (6)	Pre-morbid measure of intelligence. This test requires people to pronounce words that do not follow the usual rules of pronunciation.
PANNS	Positive and Negative Syndrome Scale	Structured clinical interview to assess positive and negative symptomatology.
PET	Positron Emission Tomography	Method of functional brain mapping based on measuring cerebral blood flow.

PSE	Present State Examination	Clinical standardization of diagnostic criteria based on structured interview (Wing *et al.*, 1974).
ROI	Region of Interest	Specific brain region investigated in a fMRI analysis, as opposed to a whole brain volume analysis.
SANS	Scale for Assessment of Negative Symptoms (7)	Scale for assessing the negative symptoms of schizophrenia.
SAPS	Scale for Assessment of Positive Symptoms (8)	Scale for assessing the positive symptoms of schizophrenia.
SPECT	Single Photon Emission Computerised Tomography	Method of functional brain mapping based on measuring cerebral blood flow.
SPM	Statistical parametric mapping	Software used to analyse structural and functional brain images.
TLC	Thought, Language and Communication disorders (9)	A scale for measuring disordered thought, language and communication abilities in schizophrenia.
ToL	Tower of London (10)	A test developed to explore and identify impairments of planning processes specific to the frontal lobe.
ToM	Theory of Mind	The ability to understand the mental states (beliefs, desires, wishes and intentions) of other people. Often referred to as Mentalising.
WAIS-R	Weschler Adult Intelligence Scale-Revised (11)	Neuropsychological instrument for assessing adult intelligence.
WCST	Wisconsin card sorting test	Test that studies the visuo-spatial components of working memory.
WMS-R	Wechsler Memory Scale-Revised (12)	Neuropsychological instrument for assessing adult memory capabilities.

Definitions

Term	Description/definition
Atypical neuroleptics	A new class of anti-psychotic drugs, which are said to have a kinder side-effect profile, and possibly to be more effective, than traditional neuroleptic medication.
Cognitive deficit	A gross, content-independent deficiency of a fundamental cognitive process, such as attention or memory. Often attributed to brain damage, cognitive deficits may also reflect general motivational deficits.
Delusion	A bizarre or irrational belief.
Endophenotype	Or intermediate phenotype, a term used to describe measurable traits that represent internal or intermediate phenotypic expression of underlying genetic susceptibility to disease.
Executive function	Set of cognitive processes involved in actively maintaining and manipulating information in order to guide behaviour (e.g. volition, planning, purposive action and effective performance).
First order false belief	Ability to represent someone else's mental state.
Hallucination	Usually defined as a perception in the absence of an appropriate stimulus. The most common example being hearing a voice when no one is present to account for it.
High-risk study	A type of study in which individuals thought to be at special risk of developing a disorder are followed up over a period of time to see if they actually become ill, and to identify factors that predict the onset of the illness. The most common variant of this type of research starts with young people known to be at genetic risk because they have a first-degree relative who is suffering from the disorder.
Mentalising	Understanding the mental states (beliefs, desires and intentions) of other people.
Negative symptoms	Symptoms characterized by the absence of desirable behaviours or experiences; for example social withdrawal, flat effect, anhedonia and apathy (avolition).
Neuroleptic (antipsychotic) medication	The class of drugs first identified in the late 1940's and early 1950's, which are known to have an ameliorative effect on positive symptoms, and to reduce the risk of psychotic relapse. They have numerous side effects.
Neuropsychological Tests	Psychological tests devised to detect different types of brain damage. Test designers administer a large number of tests to patients with different types of brain damage and select items on which patients suffering from the type of brain damage of interest perform poorly. In the case of certain types of diffuse damage, neuropsychological tests

	may be more sensitive than brain scans.
Paranoid delusions	Delusions of persecution, reference, misinterpretation and thoughts being read (third-person auditory hallucinations).
Passivity	Delusions of control, delusions of influence, thought insertion, thought withdrawal, second-person auditory hallucinations.
Positive symptoms	Symptoms that consist of experiences and behaviours that would preferably be absent such as delusions and hallucinations.
Remission	Minimum 2-week period free of signs and symptoms.
Second order first belief	Ability to represent someone else's thoughts about another's mental state.
Self-monitoring	The process of determining the likely source of a cognition or action. Also referred to as source monitoring.
'State' effects	Effects related to phenotypic expression of disease. In the current study, since no subjects met criteria for schizophrenia at baseline, this term is used to describe effects related to the manifestation of some of the characteristic features of the disorder rather than the disease itself. See also 'trait' effects.
Symptomatology	The combined symptoms of a disease.
Time series	Series measurements that occur over time, for example a series of brain scans.
'Trait' effects	Effects of presumed genetic origin.
Voxel	A volume element. The smallest, box shaped part of a three-dimensional space.

Summary of organisation of thesis

The overall aim of this thesis was to investigate Theory of Mind (ToM) and self-monitoring abilities in individuals at enhanced risk of schizophrenia. Specifically, whether any compromised abilities were of a trait nature, due to being at enhanced risk status, or of a state nature, due to the presence of current and previous psychotic symptomatology. Two investigative modalities were utilised, a battery of neuropsychological tasks and a functional magnetic resonance imaging (fMRI) visual joke paradigm. The thesis chapters are accordingly divided between these two research methods. The first two chapters pertain to the neuropsychological aspect of this thesis. Chapter 1 introduces ToM and how it has been investigated through neuropsychological tasks within schizophrenia thus far. Chapter 2 details the neuropsychological ToM and self-monitoring investigations and consequent findings conducted on the high risk individuals recruited for this thesis. The following three chapters concern fMRI, with Chapter 3 defining and describing fMRI and how the derived data is analysed, followed by a review of the ToM imaging literature. Chapter 4 describes the neuropsychological pilot study of the fMRI stimuli whilst Chapter 5 details the visual joke fMRI paradigm used in this investigation.

Chapter 6 is a general discussion drawing together the major findings from the two investigative modalities and discusses the limitations of the work undertaken in this thesis and possible future research.

Publications

Marjoram D, Miller P, McIntosh AM, Cunningham-Owens DG, Johnstone EC & Lawrie SM. **A neuropsychological investigation into 'Theory of Mind' and enhanced risk of schizophrenia.** *Psychiatry Research, In Press.*

Marjoram D, Job D, Whalley H, Gountouna V-E, McIntosh AM, Simonotto E, Cunningham-Owens D, Johnstone EC & Lawrie SM. **A visual joke fMRI investigation into Theory of Mind and enhanced risk of schizophrenia.** *NeuroImage 2006 31 1850-1858.*

Marjoram D, Gardner C, Burns J, Miller P, Lawrie SM & Johnstone EC: **Symptomatology and social inference: A theory of mind study of schizophrenia and psychotic affective disorder.** *Cognitive Neuropsychiatry* 2005 10 (5) 347-359.

Marjoram D, Tansley H, Miller P, MacIntyre D, Cunnigham-Owens D, Johnstone EC & Lawrie S: **A Theory of Mind investigation into the appreciation of visual jokes in schizophrenia.** *BMC Psychiatry* 2005, 5:12.

Abstract

Schizophrenia is a highly heritable disorder that usually becomes manifest in early adult life. With a worldwide incidence of 1%, this debilitating form of psychosis is generally characterised by the presence of delusions and hallucinations. The established condition has been associated with structural and functional brain abnormalities and neuropsychological deficits in several cognitive domains. One of these, Theory of Mind (ToM), is the ability of individuals to correctly infer the intentions and behaviours of others. It is a necessary component of social cognition for successful interaction in the social milieu. This ability has been found to be compromised in individuals with schizophrenia. It has not yet been fully elucidated whether this is a state effect that fluctuates with symptom severity (particularly those of delusions and hallucinations) or a trait effect that stems from being at risk of the disease.

The Edinburgh High Risk Study is a longitudinal study (1994 -2005) into individuals at enhanced risk of schizophrenia, so called as they have first and second degree relatives with the disease. The study has employed serial clinical, neuropsychological assessments and structural and functional magnetic resonance imaging (fMRI) in order to track changes over time in individuals who develop the disease. One of the findings of the study was that a large proportion of the High Risk participants reported isolated or transient psychotic symptoms (nearly always either a type of delusion or hallucination) during clinical interview.

The aim of this thesis was to investigate ToM abilities in these high risk individuals through a battery of ToM and self-monitoring neuropsychological tasks and a visual joke fMRI paradigm. A sample of the larger EHRS cohort was recruited. The High Risk participants were split into two groups on the basis of the presence or absence of positive psychotic symptoms. HR+ (n=12): individuals who had reported transient psychotic symptoms in at least one PSE interview during their participation in the EHRS.

HR- (n=13): individuals who had never reported any psychotic or transiently psychotic symptoms or otherwise, during PSE interview.

Controls (n=13): matched individuals with no family history of schizophrenia. Trait effects were examined by comparing the combined HR groups to the controls whilst state effects were investigated by comparing the two HR groups both to each other and the controls.

For secondary analyses investigating symptomatology, the HR+ group was then further split into the following two groups based on past or present psychotic symptoms. HR+Now (n=6): individuals who reported transient psychotic symptoms on the day of testing. HR+Ever (n=6): individuals who had reported transient psychotic symptoms in a previous clinical interview but not in the one on the day of testing. In addition, a group of five individuals (HRill) who had initially been high risk but had developed schizophrenia were recruited.

On the ToM neuropsychological tasks, significant group differences were observed in two of the three tasks for the HR+ group, particularly in those who had experienced symptoms at or around the time of testing (HR+Now). The observed ToM deficits appeared to be primarily related to state effects rather than trait effects.

The fMRI task provided robust activations across the groups in areas previously associated with ToM abilities in the literature. Significant between group activations were observed in the Prefrontal Cortex (PFC), with the HR- activating significantly greater than the HR+ in these regions. Both the secondary state specific analysis and a third post hoc analysis further investigating state effects showed significant PFC between group differences. The observed PFC dysfunction in the HR+ groups is interpreted as the neural correlate for the compromised ToM ability seen in the neuropsychological tasks.

In conclusion, this study has shown that ToM abilities in a sub sample of the EHRS cohort appear to be related to the presence of positive psychotic symptoms. Individuals with symptoms at or around the time of testing were more impaired than those who had such symptoms in a previous assessment, who in turn were more impaired than those High Risk participants who had never experienced such symptoms during their participation in the EHRS. This study is the first time schizophrenia relatives have been imaged using a ToM paradigm and the results provide evidence of both a state and state mediated trait effect. These findings generally provide support for the state theory of ToM impairment.

1 Theory of Mind (ToM)

1.1 Social Cognition

Human beings are highly complex social beings that interact with a large number of people continually on a daily basis and across their lifetime. The ability to successfully interact with individuals and groups, (be it family members, friends, work colleagues through to strangers at the bus stop) is a vital part of human life. Indeed, the reproductive success of our ancestors depended on their ability to negotiate the social milieu and compete (successfully as our presence attests) with members of their own species. Social cognition is the term for this aspect of our cognitive capabilities and can be described as the domain of cognition that involves the perception, interpretation and processing of social information. It refers to the processes that subserve behaviour in response to conspecifics (13) and can be further defined as the processing of any information which culminates in the accurate perception of the dispositions and intentions of other individuals (14). It not only refers to the ability of people to make sense of other people, but of themselves as well (15). The social brain hypothesis states that the brain has evolved specific mechanisms for dealing with the demands of complex interactions. Indeed, it has been postulated that species group size drives encephalization such that larger groups demand larger brains, particularly cerebral cortex (16). Thus, social cognition is a broad concept and incorporates all aspects of social functioning from perceiving social stimuli (e.g. emotion and face processing) to attributional style and Theory of Mind (15).

1.2 Theory of Mind

1.2.1 Introduction

This crucial aspect of social cognition is defined as the ability of an individual to understand that other people have minds different from our own and to be able to infer the beliefs, wishes, desires and intentions of other people in order to predict, and in some cases, control their behaviour. An interaction can be said to be successful, or rewarding when erroneous predictions are minimal (17). Theory of Mind (ToM) was first coined by Premack and Woodruff (18) regarding their primate investigations. However, the term has been called a useful but misleading shorthand (19) as if taken at its most literal, the term 'theory' incorrectly implies that a child theorizes about the nature of feelings, wishes, beliefs, desires etc (20). In this way, the terms mind-reading (21) and mentalising are used synonymously with it. In this thesis, the terms mentalising and ToM will both be used to describe the cognitive mechanisms that allow one to predict and interpret the behaviour of people based on the understanding of their minds.

Studies investigating ToM abilities in monkeys, apes and humans suggest that it is humans and some species of ape who have theory of mind but not monkeys (as to whether primates and other species do have ToM capabilities is beyond the scope of this thesis). This implies that new brain regions or systems have evolved that underpin these abilities (19). Mentalising abilities probably arose in the late Pleistocene period in hominids as individuals were required to cope with an increasingly complex social environment (22,23). It has been proposed that the

neural system underlying ToM most likely evolved from the capacity to monitor biological motion such that monitoring the behaviour of conspecifics may have formed the basis for the evolution of monitoring others' minds (23). The cost of this cognitive domain is that the evolution of a big brain is energetically expensive and the ontogenetic acquisition of mentalising abilities is extremely time-consuming (24).

1.2.2 Development of ToM

We are not born with a fully functioning ToM capability but a system of developmental precursors. The conceptual framework of agency, intentionality and mind probably occur from perceptual discrimination in infancy, between birth and 18 months. A succinct summary of the stages of ToM abilities is as follows:

At birth we have a capacity to imitate. By 9 months there is reliable evidence of children's perceptual sensitivity to self-propelled movements and to goal directed action. By 14 months a child has the ability to parse human action streams into meaningful intention-relevant units, (25). At 18 months a child can associate "seeing" with "knowing", use protodeclarative pointing gestures and engage in pretend play and recognize themselves in a mirror (23). At 2 years of age there is a conceptual understanding of desire, by age 3 a conceptual understanding of belief and this culminates in the understanding of false belief at age 4-5 years, considered by many to be the watershed of ToM development. This ability of a child to distinguish between their own and another persons belief, and to be aware that another person may hold false beliefs that do not match the child's own knowledge is commonly referred to as a first order false belief. At 5-6 years, children learn to

understand higher order representations, for instance, a second order belief is to know that someone else thinks that a third person believes something (23,26). Faux pas, the capacity to understand a situation in which one character should have kept information from another, is an unstable ability in children before the age of 10, with girls apparently able to understand this sooner than boys (23). Understanding a faux-pas situation requires the person to have a mental representation that the person saying it does not know that they should not say it, and another that the person hearing it would feel insulted or hurt. Thus recognizing a faux-pas situation involves inferring cognitive-mental states (thoughts) as well as an empathic inference about how the person would feel (27). Sarcasm and irony comprehension occur later still.

Mentalising abilities evolved in humans in order to cope with a social environment that is in many ways fundamentally different from our present social environment (e.g. we have much a much larger social network today) and this coupled with unfavourable social conditions during early childhood provides many possible impediments for proper ToM development (24).

1.2.3 Language and ToM

In adult social behaviour, language is an important vehicle by which ToM skills are expressed and put to use. As with the age old chicken and egg scenario, people are divided on whether language precedes or follows ToM. Dunbar (28) suggests that language evolved as a bonding device based on the exchange of social information concerning relationships within the social network. According to the social linguistic view, development of mental-state understanding follows from language development and social interaction. To develop language (including both its

pragmatic and syntactic dimensions) is itself to develop a representational system and a set of representational and interpretative practices which themselves are preconditions of the attribution of mental states to others and to ourselves (29). Others suggest that having the ability to infer others' communicative intentions are a precondition for language hence ToM development precedes language development (25,30,31). Recently, several studies of mentalising abilities in individuals with schizophrenia have reported that a violation of the rules of pragmatic use of language is linked to patients' impaired ToM (32-35). Regardless of which way round it indeed is, as thought and speech are verbal, then language and ToM are inextricably linked.

1.3 Theoretical conceptualizations of ToM

There are several different current theoretical conceptualizations regarding the cognitive architecture of ToM. A current and key debate in the existing literature concerns the degree to which ToM depends upon specialized processes, devoted to the purpose of ToM computations (domain-specific processes) or upon processes such as language and executive function that also serve other cognitive functions (domain-general processes (36)).

1.3.1 Self versus others ToM

Self-awareness can be broadly defined as the ability to reflect one's own thoughts (37) and this may in turn lead to greater understanding of someone else's mental states (38). There are two types of self-awareness: private self-awareness is one's

awareness of ones own feelings, thoughts, and motives, whereas public self-awareness is one's ability to understand how other people view themselves socially (39). Evidence for the relationship between self-awareness and ToM is that in human development, self-awareness (as measured by several factors, including self-pronoun use and mirror-recognition) precedes the development of ToM (40). And secondly, in populations where there is a self-awareness deficit (e.g. schizophrenia and autism) there is evidence of ToM deficits (41).

1.3.2 Modularity

In the same vein as Fodor's (42) concept of a modular organisation of the human brain, Leslie (43) proposed the existence of a ToM module (ToMM) which is alleged to process information restricted to social information. It is an innate, encapsulated part of the core architecture of the human brain and is domain specific in that it is specialized for learning about mental states. According to this view, the representational system of 'theory of mind' comes on-line during the second year of life. The accurate functioning of the ToMM depends on what is called a selection processor (SP) to separate relevant from irrelevant contextual information and therefore increase the likelihood that a person's inference of others' mental states is correct (23,44,45). Scholl and Leslie state that a module is not thought to exist full-blown in the mind of a neonate, but must be triggered by the environment during maturation (44).

The massive modularity theory proposes a model of human mind architecture based on modules. The mind is comprised of a large number of these modules, such as ToM, and each has been shaped by natural selection to perform specific tasks (46).

This proposed modularity of ToM is similar to that of Chomsky's (47) model of a language acquisition device that is innately pre-programmed to recognize language and test linguistic input against a constrained and preordained set of test hypotheses about language structure (29).

There are several arguments for the innateness of ToM. Firstly, its acquisition by normal children is characterised by a relatively fixed developmental sequence. Secondly, full-blown ToM appears to have obvious developmental precursors (e.g. shared attention mechanism and ability to discriminate maternal voice) which are themselves clearly innately determined. There appears to be a double dissociation of ToM from general intelligence. It is observed that children with Downs's syndrome develop ToM at relatively normal mental ages whilst children with autism and comparable or higher IQ's frequently fail to develop ToM. Moreover, ToM development can appear normal despite a gross impairment of most other cognitive functions (29). Some argue that ToM is acquired through the acquisition of social and linguistic competencies and does not precede them as an autonomous body of knowledge (i.e. it is an acquired module). They believe that language and social skills may be largely innately determined and strongly modular but that ToM itself does not constitute an innately determined module (29). It does seem clear that input from the social environment clearly facilitates cognitive and consequent ToM maturation. Studies have shown that young children whose parents frequently use expressions referring to mental states when talking to them pass ToM tests at an earlier age than children whose parents use such terms less often. Furthermore, the

presence of older siblings appears to further facilitate the speed at which young children understand other minds (23).

1.3.3 Theory theory

This perspective is primarily a non-modular model and is 'metarepresentational' in nature and was first proposed by Premack and Woodruff (18) who suggested that the acquisition of ToM capacity is based on the development of a theory, e.g. a set of principles used to explain and predict behaviour. This model proposes that infants and children acquire different levels of representational skills in steps during ontogeny, starting out with primary levels of the self as an acting agent (48). Experience provides infants with information that cannot be accounted for by their present theory of mind and this will eventually cause them to revise and improve that theory (49). In contrast to the strict modular model, the metarepresentational theory holds that the differentiation between reality and mental models may underlie not only ToM but also the more general capacity to "collate" multiple mental models simultaneously. There is a lower level computational architecture that is comprised of domain specific mechanisms, the outputs of which are used for inferences by higher level domain general mechanisms. There is no specific ToM module, rather ToM abilities are alleged to depend on the interaction (both developmental and on-line) of domain-general abilities with lower-level cognitive mechanisms for representing social information (e.g. face processing, gaze monitoring, tracking of intentions and goals, joint attention (50)). The theory-theory model therefore maintains that metarepresentational skills are not necessarily restricted to the execution of ToM (23).

1.3.4 Simulation theory

This model of mentalising abilities, first proposed by Harris (51) considers ToM as innate and intuitive rather than the result of learning and experience. It is based on taking someone else's perspective, imaginatively 'putting ourselves in another person's shoes' via projecting ones own attitudes on someone else. Attributing mental states to oneself is at the core of inferring the mental states of others by replicating or mimicking the mental life of other individuals. Thus, the capacity to develop self perspective would be reduced to a subcomponent of a more general ToM capacity. Both capacities would be functionally closely related and should employ the same neural mechanisms (23,48).

Before discussing the ToM literature in relation to schizophrenia it will first be necessary to briefly define both autism and schizophrenia.

1.4 A brief overview of autism

The ToM investigations into schizophrenia derived from the investigations of the ToM abilities of children with autism. This is a neurodevelopmental neuropsychiatric disorder which is characterised by severe and sustained impairment in social interaction, deviance in communication and patterns of behaviour that are restricted and/or stereotyped. Onset is by definition before age 3 years (52). Some of these signs, such as social withdrawal, stereotyped behaviour and lack of communication are both typical features of childhood autism and of chronic negative features of schizophrenia (53). There are three current theoretical approaches to autism that try

to explain the observed symptoms and behaviour. It could be an executive function dysfunction (impairment of problem solving, forward planning and organisation skills), weak central coherence (difficulties integrating information into meaningful wholes) or a ToM deficit. The latter proposal has found a large body of support. According to Frith et al., (54,55) in the normally developing child the computational capacity to represent mental states has an innate neurological basis but in the autistic child, neurological damage to a circumscribed system of the brain has occurred. Autistic children exhibit a triad of behavioural and cognitive symptoms consisting of of social aloofness, language difficulties and deficient imagination. These symptoms cause a child with autism to remain socially aloof from family conversational partners, have too few linguistic skills to be able to converse with family members about false or abstract ideas, and lack the imaginative capacity that is necessary in order to fully appreciate someone else's beliefs (29). Possible limitations to this ToM theory are the strong relation of ToM abilities to language and the fact that many high-functioning individuals with autism can compete usual ToM tasks and yet have striking social difficulties (52).

1.5 A brief overview of schizophrenia

Schizophrenia is a serious debilitating psychiatric disorder which is characterized by chronic positive psychotic symptoms (delusions and hallucinations) and psychosocial impairment which can result in the breakdown of cognitive control of action and the presence of disorganised and socially inappropriate behaviour. With an age of onset around age 25 years, and usually a lifelong course characterised by cycles of relapse and remission, it exacts considerable human and economic costs.

The illness was originally described by Kraepelin as a clinical syndrome and termed 'Dementia Praecox' (56) with a relatively young age of onset and typical deterioration after time. Bleuler later re-named it schizophrenia (57) in order to describe a split or disintegration of associations between different cognitive processes. Bleuler did not consider hallucinations and delusions as primary in the disorder. Half a century later, Schneider, by identifying those characteristics peculiar to schizophrenia, shifted the focus to such symptoms which are referred to 'first rank' symptoms (58). There are nine in total, only one being required to be present for a diagnosis of schizophrenia.

The disease takes a characteristic course, with a prodromal stage preceding the onset of psychosis. Symptoms can be divided into three main categories of positive or 'psychotic' symptoms (delusions, hallucinations and thought disorder), negative or 'deficit' symptoms (severe disturbances in social interaction, motivation, expression of affect, ability to experience pleasure and spontaneous speech) and cognitive impairment (deficits in executive function, attention, memory and general intellectual functioning, (59)). Studies have shown that negative symptoms are more stable than positive symptoms and are less likely to improve over the course of the illness (60). Although some individuals recover symptomatically from the first episode, the majority proceed to have one or more subsequent episodes in the form of psychotic relapses from which a large proportion fail to recover, at least to the same degree as they had during their first or prior episode. This process of psychotic relapses, treatment failure, and incomplete recovery leads many patients to a chronic course of illness with persistent deficits and disturbances in thought processes and cognition (61). The chronicity of the condition typically leads to a heavy burden on health care,

welfare and relatives, producing a large economic and emotional burden to society and the afflicted families respectively.

The age of onset is usually in adolescence and early adulthood with an earlier onset in males (20-24yrs, (62)) than females who usually have an age of onset a few years later (53). Despite this discrepancy in the age of onset, the incidence of the disease is equivalent across the genders (63).

Currently, the diagnosis is made depending upon the description and observation of the patient's mental state using two standardised criteria manuals; Diagnostic and Statistical Manual of the American Psychiatric Association (DSM IV) (64), or the International Classification of Diseases (ICD-10 (65)). There is continued debate as to the validity of the term schizophrenia with symptoms varying widely between patients and the fact that there is not one single psychopathological symptom, biochemical or structural marker that is specific or unique to schizophrenia (20,66).

Schizophrenia is widely considered to be a genetically mediated neurodevelopmental disorder. The world-wide lifetime risk is 1% but this is greatly increased amongst first degree relatives: 9% for a sibling of an affected individual and 13% for a child of an affected parent (67). The risk of the second twin of a monozygotic pair developing schizophrenia is 28% whilst that for the second dizygotic twin is the same as for ordinary siblings. These figures do not represent Mendelian inheritance and it is highly probable that environmental factors (e.g. cannabis and stress) potentially modulate the expression of symptoms. Many genes have been implicated, with the possibility of gene-gene interaction and a diversity of genetic causes in different families and populations (59). A neurodevelopmental rather than degenerative process has received more empirical support as a general explanation of

the pathophysiology. Examples of evidence pertaining to this are neurobiological deficits observed at the time of disease onset, lack of the normal pathological response of the central nervous system to brain insults (namely gliosis) and the findings that individuals who later go on to develop the disorder show behavioural disorders in childhood (68,69). This developmental disorder theory is apparent along two dimensions: the combined genetic and environmental continuum, and the maturational continuum, which continues to impact at various developmental stages throughout life, most notably in early adulthood, prior to the onset of psychosis. Schizophrenia is increasingly viewed as a disconnection syndrome, in which the inter-regional communication in the brain is compromised, as opposed to a localised deficit in any one region. The mechanism of action of anti-psychotic treatments therefore presumably involves the modulation of inter-regional functional connectivity (70) as well as known effects on dopaminergic neurotransmission.

Structural brain changes are present in vivo and post-mortem, with histopathological and imaging studies revealing that temporal and frontal lobes are the most affected regions. Functional imaging, neuropsychological testing and clinical assessment also demonstrate deficits in cognition, and these observed deficits can be correlated with abnormalities in the areas of the brain with structural abnormalities (59,71).

Taking into account the neurochemical and psychopharmacological investigations into both autism and schizophrenia, it has been hypothesized that ToM abilities are contingent on the integrity of the dopaminergic and serotonergic (DS) brain transmitter systems. The trait-state nature of ToM impairment in these two disorders is probably due to specific abnormalities in the neurochemistry of the DS system within them (72).

1.6 Delusions and Hallucinations

These two phenomena are the basis of positive symptoms in schizophrenia.

A delusion can be defined as a bizarre or irrational belief, in essence, a false belief, which is out with cultural norms and does not yield to contrary evidence. Hallucinations can be similarly simply defined as perceptions in the absence of a stimulus, a common example being hearing a voice when no one is present to account for it (53). In this way, hallucinations can be described as false perceptions. Delusions and hallucinations can occur in isolation from one another but often do occur together. It has been proposed that they are both capable of influencing and facilitating each other e.g. an individual can make a delusional interpretation of a hallucinated voice and hallucinations can be facilitated by certain types of belief (20).

Hallucinations tend to reflect the expectations and preoccupations of the patient (53). Input theories of hallucinations state that a hallucination occurs when an external stimulus is misperceived (possible failure of discrimination or an abnormal bias) whilst output theories state that a patient is talking to themselves but perceives the voices as coming from elsewhere (53).

There are currently three contemporary theories of delusions. Frith (53) proposed that delusions of reference and of persecution (and third person auditory hallucinations) arise from an inability to represent the beliefs, thoughts and intentions of other people, a ToM deficit. Garety and others argue that the literature indicates that delusions are unlikely to share a common cause but that a number of factors contribute to them (e.g. past experience, affect, self-esteem and motivation) and have set out a multifactorial model which incorporates probabilistic reasoning biases (73).

Bentall et al (74) propose that they arise from an attributional bias (e.g. people with persecutory delusions externalise blame for negative events). Some types of delusion involve impairment of normal mentalising abilities. Indeed, there is something very redolent of theory of mind about persecutory delusions, which inevitably involve mistaken assumptions about the intentions of other people (20). Delusional disorders have been labelled 'Theory of Mind' delusions by some researchers because they seem to involve inferences (or theories) about what is going on in the minds of other people (e.g. (75).

Within the Edinburgh High Risk Study (EHRS), many more participants than the number who went on to develop schizophrenia, reported isolated or transient psychotic symptoms (delusions and hallucinations in the main). These symptoms were used to split the high risk relatives into sub-groups on the basis of presence or absence of these symptoms in the analyses later reported in this thesis. Research into such symptoms in the general population show that they can be present at varying levels, ranging from 4% (76) up to 10% (77). Investigations into the EHRS cohort have shown that within the cohort which consists of people with a high familial risk of schizophrenia, this lies nearer to 40% (78). In the Dunedin study cohort, another longitudinal investigation into schizophrenia, 25% of participants reported such symptoms (79). Table 1.1 shows example of positive symptoms associated with schizophrenia.

Table 1.1 Major positive symptoms associated with schizophrenia. Taken from Frith (1992).

Thought insertion	Patients experience thoughts coming into their mind from an outside source. Example: Thoughts are put into my mind like "Kill God". It's just like my mind working but it isn't. They come from this chap Chris. They're his thoughts.
Thought broadcast	Patients experience thoughts leaving their mind and entering the minds of others. Example: It was like my ears being blocked up and my thoughts shouted out.
Thoughts spoken aloud/thought echo	Patients hear their thoughts spoken aloud, sometimes just after they have thought them.
Thought withdrawal	Patients experience their thoughts being removed from their head.
Third person auditory hallucinations	Patients hear voices discussing them in the third person, sometimes commenting on their actions. Example: I hear a voice saying "He is an astronomy fanatic. Here's a taste of his own medicine. He's getting up now. He's going to wash. It's about time."
Second person auditory hallucinations	Patients hear voices talking to them. Example: I hear a voice saying, "You're not going to smoke the cigarette the way you want to."
Delusions of control	Patients experience their actions as being controlled by an outside force. Example: The force moved my lips. I began to speak. The words were made for me.
Delusions of reference	The actions and gestures of strangers are believed to have special relevance to the patient. Example: I saw someone scratching his chin which meant that I needed a shave.
Paranoid delusions	Patients believe that people are trying to harm them. Example: People at work are victimising me. A bloke at work is trying to kill me with some kind of hypnosis.

1.7 Neuropsychological investigations

Neuropsychological tests are psychological tests devised to test different types of brain damage/cognitive impairment. Test designers administer a large number of tests to patients with different kinds of brain damage and select items on which patients suffering from the type of brain damage of interest perform poorly (20). Indeed, neuropsychology was originally a method of detecting and localizing specific brain lesions. In this way, general tests of intelligence led on to the development of comprehensive neuropsychological test batteries which included sub-tests of what was described as frontal, temporal or parietal lobe function. This 'location-ism' has recently been recognized as over-simplistic, both for most tasks and for most psychiatric patients. Researchers have taken to referring to particular abilities and 'modules'. In addition, some have devised 'everyday' tests of these domains that might more accurately reflect the daily living problems of neuropsychiatric patients than do tests devised to identify sites of gross brain damage. Cognitive neuropsychology is a recent field in this research area in which attempts are made to explain symptoms or the disease as a whole in terms of abnormal cognitive processes, often as measured with inventive novel tests for each particular experiment (80). In the case of diffuse damage, neuropsychological tests can be more sensitive than brain scans (20).

Patients with schizophrenia show numerous deficits on neuropsychological examination. Over the past 50 years, neuropsychological assessment of patients with schizophrenia has provided evidence of both intellectual impairment and deficits across a wide range of cognitive domains, including motor, spatial ability, attention, executive function, language and learning and memory. Such an array of deficits

thereby implicates dysfunction in an equally wide range of brain networks, including the frontal, parietal, temporal lobes and the cerebellum (81).

Although patients with psychotic disorders perform poorly on just about every neuropsychological test administered, some degree of caution is warranted in interpreting these alleged deficits. It is often very difficult to decide whether poor performance reflects specific psychological processes that are affected in the patient, general intellectual deficits or the more general effects of demoralization and institutionalization. Poor performances on general measures of mental functioning may be caused by poor motivation and not just an aspect of cognitive impairment (20).

1.8 Schizophrenia symptoms and compromised ToM abilities

ToM can be described as a representation of epistemic mental states comprising an agent, an attitude and a proposition e.g. "Peter believes that it is raining" (21,82,83). This representation of the mental state of an agent (Peter, who believes it is raining) need not be affected by the proposition (it is raining), which may or may not be true (84,85). In this way, Leslie and Roth (85) proposed that a major requirement for such representations is a mechanism that decouples (43) the content of the proposition (it is raining) from reality.

1.8.1 Frith's Metarepresentation theory

Frith (53) hypothesized that positive symptoms themselves could result from impairment in metarepresentation - the ability to represent abstract cognitive

processes about oneself and others. Furthermore, Frith (86) hypothesized that in certain cases of schizophrenia something may go wrong with the above decoupling process in two ways. Using the above scenario, firstly the content (it is raining) becomes detached from the rest of the proposition (Peter believes that...) and secondly, the content is perceived as a representation of the real world rather than someone's belief about it. This statement, unattached to any implication that it is a thought or belief of the patient, or indeed another person, may then be misconstrued (e.g. as a third-person auditory hallucination). Different forms of hallucination may be experienced according to the precise propositions misperceived. Misinterpretation of the behaviour or intentions of others may manifest as the delusions of reference, misidentification and persecution, experienced by some schizophrenic patients.

Furthermore, Frith (53) proposed that people with schizophrenia resemble people with autism in so much as they also have a compromised mentalising mechanism. However, the manifestation of this will be different in both disorders. In the autistic individual they will never have developed a theory of mind and will consequently not realize that other people have minds different to themselves. Similarly, in schizophrenia patients with chronic negative features, it is alleged that, similar to autism, ToM impairment in this schizophrenia subgroup is nontransient. There are several proposed reasons for this. Firstly, patients belonging to this group reportedly have social and cognitive abnormalities in early childhood during which time normal ToM development occurs. Secondly, early neurodevelopmental abnormalities have been linked to patients with this type of schizophrenia. Finally, these patients are reported to be refractory to medication and hence cognitive abilities including ToM impairments could therefore be irrecoverable (17). On the other hand, individuals

with the positive symptoms of schizophrenia will have developed ToM abilities and will consequently appreciate that other people have minds distinct from theirs; however they will have lost this ability to infer about the intentions of others minds and in some cases will also lose the ability to reflect on the content of their own mind. They will however know well from past experience that it is useful and easy to infer the mental states of others and will go on doing this even when the mechanism no longer works properly and incorrect inferences pertaining to other people's beliefs, desires, wishes and intentions will therefore occur.

Frith's metarepresentation model predicts that patients differ in their ToM abilites depending on whether objective (behavioural) or subjective (experiential) symptoms prevail. Frith (53) outlined three areas of self consciousness in which metarepresentation plays a key role: awareness of our own goals, awareness of our own intentions and awareness of other people's intentions. Consequently, these three areas correspond to three types of cognitive impairment underlying the signs and symptoms of schizophrenia:

Without awareness of goals there is poverty of will. This leads to negative and positive and behavioural abnormalities.

Without awareness of intentions there is lack of high level self-monitoring. This leads to abnormalities in the experience of action.

With faulty awareness of the intentions of others there are delusions of persecution and delusions of references.

This model is not without its critics however, Gallagher (87) provides a neurophenomenological critique of this theory to which Frith is sympathetic to (88).

How positive symptoms, particularly those of delusions and hallucinations, actually interfere with ToM capabilities is not known and it remains to be elucidated whether there is a special relationship between mentalising capabilities and symptoms (89). This metarepresentation hypothesis best fits the modular theory of ToM abilities (23).

1.8.2 Hyper ToM

Indeed, it can be said that rather than a deficit of ToM in these individuals with positive symptoms there is actually an excess of ToM (17), as an intact theory of mind mechanism is needed, say, to generate persecutory delusions and there is an over attribution of intent. This can result in a 'hyper ToM' (17) in that they will "see" intentions to communicate when there are none (delusions of reference). They may start to believe that people are deliberately behaving in such a way as to disguise their intentions. They will deduce that there is a general conspiracy against them and that people's intentions towards them are evil (paranoid delusions).

Using this hyper ToM concept, a mental state impairment continuum can be envisaged (17,90). Through the research on mentalising ability in autism, autistic spectrum disorders and schizophrenia, ToM impairments have been characterized on a continuum where a specific impairment can be characterized as having:

No representational/conceptual understanding of mental states (e.g. autism).

Representational understanding of mental states, but a deficit in the ability to apply/manifest this understanding (e.g. Asperger's syndrome and negative symptom schizophrenia).

Representational understanding of mental states, but abnormal attribution/application of these mental states (e.g. delusional and paranoid schizophrenia).

Intact representational understanding of the mind of others but impaired self (e.g. schizophrenic patients with passivity phenomena).

1.8.3 Hardy-Baylé's disorganization theory

Hardy-Baylé (91), in contrast to Frith, argues that compromised ToM abilities in individuals with schizophrenia arise from a deficit in executive function and planning. According to this theory, it is those individuals with highly disorganised thought, language, and communication skills, the TLC scale (92) who are predicted to perform most poorly on ToM tasks. This is due to their inability to not only monitor their own actions but also to adequately represent other people's mental states and to integrate contextual information (23,93). The absence of a mental representation of a patient's own intended action would also compromise a patient's capacity to assign mental states to other people's actions. In this way, this model expects to observe ToM deficits exclusively in patients with prominent thought and language disorganisation, whilst relatively intact ToM abilities are expected in those patients without disorganisation symptoms. This proposed model would best fit the simulation theory of ToM (23).

1.9 ToM neuropsychological tasks

Neuropsychological ToM investigations into schizophrenia originally stemmed from the ToM studies into young children and autism. These tasks were designed to test false beliefs (the ability to understand that other people can hold false beliefs that are different and incorrect to one's own correct knowledge) and often used a

combination of both physical props and verbal description, and were succinct. Such an example is the seminal Sally and Anne Test (originally called Maxi and the chocolates; (94)). This task involves the experimental creation of a situation in which a test participant has to distinguish his/her knowledge that an object that has been hidden by one character (Anne) in the absence of another person (Sally) from the knowledge of the other characters involved. The crucial question of this scenario (often enacted through props of two dolls) is where Sally will look for the hidden object on her return, the place where she initially hid it or the place to which it has recently been moved by Anne. This question tests first order false belief in that it requires the ability to metarepresent Sally's mental state. An example of a scenario investigating second order false belief is the ice cream van task (95). Success on these types of ToM task involves inhibiting the potent choice of the real location of an object, and choosing instead the false location that would be represented in the mind of a person with false belief (96,97).

These tasks used for children were deemed too easy for adults and new and innovative tasks were conceived and implemented in the mid 1990's. Frith and co-workers designed three different tasks that have successfully investigated adult participant mentalising abilities:

1) The Hinting task (98) tests participant's abilities to understand characters intentions via 10 short scenarios involving 2 characters, one of whom is always dropping a very obvious hint. Participants are asked to comment on the characters' intentions.

2) Participants hear six short stories involving false belief (first –order false belief tasks assess the knowledge of a story character's false belief about the world and

second-order false belief assess the acknowledgment of what one story character thinks about another story character's thoughts) and deception (99). Participants are questioned about the mental states of the involved characters.

3) Participants are shown ten visual jokes requiring mental state attribution to correctly determine the punch line and are asked to explain them (100).

Hardy-Bayle and co-workers designed a paradigm using comic strips. Subjects are asked to complete comic strips, which are intended to represent the intention or the belief of a character in a few pictures, by choosing one in a set of two (101) or three (102) answer-cartoon drawings.

1.10 Verbal vs. Pictorial Modalities

These two modalities provide different stimuli to each other. On the one hand, verbal narratives describing a scenario and character interactions whilst on the other, line drawings (usually black and white and caption less) depicting a scenario and character interactions. Cartoon drawings, whether a single image or several ordered images, like verbal narratives, can also be considered narratives as they too tell a story (19). Investigating whether there was a significant difference in performance when stimuli were of a verbal or pictorial nature, Sarfati et al., (103), found that a non-disorganised schizophrenia group, a depressed group and normal controls performed similarly in the verbal and pictorial conditions of the same task. The authors concluded that it is valid to compare the results obtained from studies that test mentalising abilities via pictorial tasks to those that use tasks of a verbal nature (and vice versa) or paradigms that use both types of task. In a later study, Sarfati et al., (104) found that half of the schizophrenia patients improved their ToM

performance after the introduction of verbal material. Those patients who did not improve were found to have a significantly longer duration of their illness.

The above tasks have provided the framework for the majority of the ToM neuropsychological testing in adults. In addition to these tasks and their variations there are more sophisticated verbal paradigms that test higher order false beliefs (e.g. second and third order), sarcasm, metaphor and irony. It is alleged that understanding metaphor requires first order ToM comprehension whilst understanding irony requires the understanding of second order false belief as this ability requires the ability to go beyond the literal meaning of utterances by inferring what the speaker actually might have intended (23).

More recent tasks of a pictorial nature include facial emotional paradigms and animations of an intentional nature.

Some of these tasks are not without their limitations or critics however, in that although they enable experimental control to be maximised they probably do have low ecological validity. That is, the problem of "real life" presentation of tasks cannot be fully satisfactorily resolved in experimental laboratory "offline" test conditions (23). Furthermore, in real life scenarios there are several cues for mentalising, such as facial expression, voice tone, body posture; whilst a paragraph of text or a cartoon depicting a false belief scenario will both be devoid of these.

Table 1.2 Chronological summary of ToM neuropsychological investigations into schizophrenia. (Based in part to the table contained in Brüne, 2005)

Study	*Population Sex Age m/f (mean yrs)*	*Tasks and measures*	*Main findings and conclusions*
(98) Corcoran *et al.*, (1995)	55 schizophrenia: 38:17 31.8 23 *paranoid* 10 *negative* 3 *incoherent* 7 *passivity* 8 *remitted* 4 *other* 14 depressed/anxious: 8:6 46.7 30 controls 20:10 31.2	Hinting Task, 10 short scenarios. IQ (Quick Test, Ammons & Ammons 1962). PSE.	Schizophrenic individuals with negative symptoms performed worst, even when IQ was covaried out. Passivity and remitted patients performed similarly to controls with patients with incoherence and paranoid symptoms in between. Results provide evidence for a state effect (symptom) on ToM ability.
(99) Frith and Corcoran (1996)	55 schizophrenia: *24 paranoid* 14:10 33.7 *12 behavioral* 8:4 33.1 *10 passivity* 7:3 31.3 *9 remitted* 7:2 31.1 13 depressed/anxious 7:6 48.1 22 controls 7:15 32.9	6 ToM stories including a first or second order false belief, with accompanying cartoon drawings. IQ (Quick Test, Ammons & Ammons 1962) PSE.	Paranoid and behavioral patient groups performed worse on the ToM task than the other clinical groups and controls. Authors suggest that due to memory problems in the former two groups, easier ToM tasks are warranted. More evidence for a state effect.
(100) Corcoran *et al.*, (1997)	44 schizophrenia: *16 paranoid* 11:5 30.1 *7 behavioral* 5:2 30.9 *8 passivity* 5:3 29.5 *13 remitted* 10:3 32.1 7 depressed/anxious 2:5 43.3 40 controls 17:23 32.2	Visual jokes: 10 physical/behavioral (non-ToM). 10 mental state attributions (ToM). IQ (Quick Test, Ammons & Ammons 1962) PSE.	Schizophrenia patients were impaired on joke appreciation. Behavioral symptom group performed worse, particularly on the ToM ones. Patients with passivity and paranoid symptoms performed worse than the control group also.

(105) Langdon *et al.*, (1997)	20 schizophrenia: 9:11 33.4 11 *chronic residual* 8 *chronic paranoid* 1 *acute paranoid* 20 controls Matched	4 four-card picture sequences of false beliefs. Social script picture sequences, mechanical picture sequences, capture picture sequences, mental state language in story narratives, self awareness block design. WAIS-R, SANS, SAPS.	Patients were impaired in monitoring both their own and others' mental states. Picture sequencing difficulties were associated with psychomotor poverty symptoms and reality distortion.
(102) Sarfati *et al.*, (1997)	24 schizophrenia: 19:5 31.9 7 *paranoid* 6 *residual* 5 *disorganised* 6 *undifferentiated* 12 depressed 3:9 41.9 24 controls 14:10 32.4	30 picture stories of a sequence of 3 with a choice of 3 for the final picture. 15 false belief 15 intention attribution stories. IQ (BPVS), TLC, SANS, SAPS.	Performance on this ToM task was found to correlate with thought and language abilities and level of disorganization. No differences were observed between the schizophrenia groups when it was classified into traditional subtypes.
(101) Sarfati *et al.*, (1997)	12 schizophrenia: 5:7 27.2 4 *paranoid* 5 *undifferentiated* 3 *residual* 12 depressed 3:9 36.3 12 controls 6:6 26.2	30 picture stories of a sequence of 3 with a choice of 2 for the final picture. 15 false belief 15 intention attribution stories. TLC, SANS, SAPS.	The schizophrenia patients could be divided into 2 groups according to their ToM abilities, normal or poor. This depended on their level of thought and language disorder. False belief tasks were significantly more difficult than attribution of intentions.
(106) Doody *et al.*, (1998)	28 schizophrenia 17:11 46.3 12 depressed 1:11 42.3 19 Learning Disabled 7:12 50.7 18 co-morbid. 10:8 50.4 20 controls 9:11 20.4	ToM stories: Sally Anne task Ice cream van task Props and maps used to illustrate tasks. ART, PANSS, IQ (Quick Test, Ammons & Ammons 1962).	The comorbid schizophrenia and learning disability group performed worse. Schizophrenia patients in general performed more poorly on second order false belief tasks than the controls and this was associated with level of psychopathology. The LD group also performed worse than the control group implying that IQ can interfere with ToM abilities.
(107) Drury *et al.*, (1998)	14 schizophrenia: 11:3 30.1 9 *paranoid* 3 *undifferentiated* 2 *disorganised*	3 second order false belief tasks, read aloud and enacted with props. Testing occurred after admission and following recovery. Substitution for co referential terms, metaphor sentence completion,	Acute schizophrenia patients performed worse than the other non schizophrenia clinical patient groups. No such difference was evident after recovery. Paranoid

	10 psychotic controls 6:4 40.7 12 depressed 6:6 42.4	interpretation of irony and metaphor. PAS and partial WAIS-R.	group with persecutory delusions performed poorly on memory tasks during acute phase, and after recovery on the second order false belief task, indicating interference of ToM abilities with both attention and memory load.
(108) Mitchley *et al.,* (1998)	18 *schizophrenia:* 15:3 45.3 13 *various psychiatric* 2:11 41.3 Matched controls	9 short written scenarios involving irony. 9 brief written scenarios involving a literal interpretation. IQ (NART) PANSS.	Schizophrenia subjects performed significantly worse than the psychiatric controls on the understanding of irony. This failure was associated with lower IQ and negative symptoms. This difference remained however, when IQ was covaried out. They were liable to interpret the ironical stories literally.
(109) Sarfati and Hardy-Baylé (1999)	25 schizophrenia: *15 disorganized* 5:10 35.7 *10 nondisorganised* 2:8 29.2 10 Manic 6:4 33.9 15 controls 5:10 28.6	14 comic strips of 3 pictures in sequence, a fourth picture had to be chosen from 4 pictorial alternatives. IQ (BPVS).	The disorganized schizophrenia performed significantly worse than the non disorganized group, manic patients and controls. Global psychopathology of this group was also investigated which provided evidence for a ToM deficit being a state effect.
(103) Sarfati *et al.,* (1999)	26 schizophrenia: *13 disorganized* 2:11 35.1 *13 nondisorganised* 3:10 30.3 Psychiatric controls 9:4 40.6 (depressed) Normal controls 2:11 33.0	Comic Strip character Intention task consisting of 28 comic strips consisting of 3 pictures; a fourth picture to be chosen from 4 alternative pictures, in a second assessment from 4 alternative sentences. PANSS IQ (BPVS) TLC.	Disorganized group was significantly worse than both other control groups and the non disorganized schizophrenia in the pictorial and verbal conditions. Performance in all four groups was significantly better in the verbal than pictorial condition. Disorganization syndrome in schizophrenia is associated with a defect in the attribution of intentions of other people.

(110) Sullivan and Allen (1999)	31 schizophrenic males 49 control males 20 schizophrenic females 44 control females	Subject Machiavellianism measured via Mach IV scale.	The schizophrenic male group, but not the female group, scored significantly lower than both the control groups.
(104) Sarfati *et al.*, (2000)	25 schizophrenia 7:18 25 matched controls	28 comic strips consisting of 3 pictures; a fourth picture to be chosen from 4 alternative pictures, in a second assessment from 4 alternative sentences.	A subgroup of schizophrenia patients were found to remediate in their ToM measures after introduction of verbal material whereas a subgroup of poor performers did not which could be a result of the chronicity of the disorder.
(111) Mazza *et al.*, (2001)	35 schizophrenia: *11 disorganized* 10:1 35.3 16 *pyschomotor poverty* 15:1 33.1 *8 reality distortion* 5:3 34.5 17 controls 1:16 37.3	2 first and 2 second order ToM tasks read loud plus cartoon drawings depicting the stories. Verbal Memory Test (Novelli et al., 1986) Verbal Fluency Test (Novelli et al., 1986) WAIS,TOL,WCST,SANS,SAPS.	The psychomotor poverty schizophrenia patients performed worse on the first order tasks and one of the second order tasks. The disorganized schizophrenia patients performed worse than the other groups and the controls on the other second order ToM task. Negative symptoms may affect metarepresentational capacities in schizophrenia independent of IQ.
(112) Pickup and Frith (2001)	41 schizophrenia: *16 paranoid* 10:6 40.9 *16 behavioral* 12:4 37.3 *1 passivity* 0:1 22.0 *8 remitted* 7:1 36.4 18 anxious/depressed 7:11 43.6 35 controls 19:16 43.3	2 first order and 1 second order ToM task enacted with props. Answers scored accorded to explanatory power and use of mental state language. 2 first order and one second order non-mental control tasks. IQ (Quick Test, Ammons & Ammons 1962) PSE.	Patients with behavioral symptoms performed more poorly on the second order false belief tasks and made less use mental state language compared to controls, independent of memory and IQ. The paranoid group performed worse than controls as well, but this effect disappeared when IQ was controlled, indicating a specific and state-dependent ToM deficit in schizophrenia.
(113) Langdon *et*	30 schizophrenia 2 schizoaffective	4 card picture sequences of false beliefs.	Schizophrenia patients had deficits in executive

al., (2001)	18:14 37.3 24 controls 12:12 34.5	Social-script picture sequences, mechanical picture sequences, capture picture sequences, visual memory. SANS,SAPS,TOL, WMS-R.	planning, disengagement and mentalising compared to controls. There was no link to positive symptoms and mentalising abilities. Furthermore, executive planning deficits did not fully account for poor ToM providing evidence for the modular hypothesis of mental state representation.
(114) Herold *et al.,* (2002)	20 schizophrenia patients in remission 20 controls	1 first order ToM task 1 second order ToM task 2 metaphor and 2 irony tasks. PANNS.	Schizophrenia patients performed significantly worse than controls only on the irony task. As these patients were in remission this deficit implies impaired ToM in schizophrenia could be a trait effect.
(115) Langdon *et al.,* (2002)	23 schizophrenia 2 schizoaffective 20 controls	4 card picture sequence of false beliefs computerized story comprehension of metaphor and irony. Social-script picture sequences, mechanical picture sequences, capture picture sequences, spot the word test. TOL WAIS-R SANS,SAPS.	Selective impairments of schizophrenia patients on ToM tasks were confirmed. Metaphor and irony understanding made independent contributions to distinguish patients from controls, suggesting divergent underlying mechanisms. Irony but not metaphor comprehension was associated with ToM abilities. Positive formal thought disorder was associated with poor performance on ToM tasks, whereas negative formal thought disorder was associated with poor metaphor understanding. Impaired ToM may relate to poor pragmatic use of language in schizophrenia.
(116) Roncone *et al.,* (2002)	40 schizophrenia: 34:10 33.4 25 *paranoid* 2 *disorganised* 1 *catatonic* 6 *undifferentiated* 6 *residual*	2 first and 2 second order ToM tasks read aloud plus cartoon drawings. IQ (SPMR) Verbal Memory Test (Novelli et al., 1986) Verbal Fluency Test (Novelli et al.,	Patients' poor ToM abilities contributed significantly to predicting their poor social functioning in the community. Duration of illness, verbal fluency, and the presence of

	4 schizoaffectives	1986) TOL,WCST,BPRS,DAS.	negative and positive symptoms also contributed to poor social functioning, with duration of illness being the strongest predictor of impaired social functioning.
(117) Brunet *et al.,* (2003)	25 schizophrenia: 19:6 31.2 4 *paranoid* 9 *disorganised* 6 *undifferentiated* 6 *residual* 25 controls 17:8 34.2	14 comic strips of 3 pictures in sequence, a fourth picture had to be chosen from 4 pictorial alternatives. 28 picture stories involving physical causality depicted. PANSS IQ (BPVS) TLC.	Schizophrenia patients performed significantly worse than controls on tasks requiring attribution of intentions. This observed deficit was found to be specific and independent of IQ.
(118) Brüne (2003)	23 schizophrenia (disorganized) 12 controls	ToM picture story involving first and second order false belief and deception. "Nonsocial" picture sequencing task.	Patients were impaired on ToM relative to controls but when IQ was covaried for this observed effect was no longer evident.
(33) Corcoran and Frith (2003)	59 schizophrenia: 50:9 40.5 16 *paranoid* 10 *negative* 10 *thought disorder* 8 *passivity* 15 *remitted* 44 controls 35:9 40.0	Hinting task ToM stories involving a first order or a second order false belief: additional cartoon drawings. IQ (Quick Test, Ammons & Ammons 1962) PSE.	Schizophrenia patients were impaired on ToM task performance. Patients, particularly those with negative symptoms, also had a poorer recall of autobiographical events compared to controls. It was found that performance on ToM tasks and autobiographical memory were related. It could be that schizophrenia patients have problems with inductive reasoning when inferring the mental states of others.
(119) Janssen *et al.,* (2003)	43 schizophrenia 24:19 32.9 (34 remitted) 41 first degree relatives 16:25 40.2 43 controls 22:21 34.8	2 short stories involving a social interaction between 2 characters and 4 hinting tasks (Frith & Corcoran 1996), tasks were read aloud. BPRS, PANSS, digit span, verbal fluency.	The schizophrenia patients performed worse than the controls with the relative group performing in between. This provides evidence for a trait effect in ToM impairment.
(120) Mazza *et al.*	42 schizophrenia: 31.3	2 first and 2 second order ToM tasks read aloud plus cartoon	Schizophrenia patients who scored well on the

,(2003)	18 *paranoid* 17 *residual* 7 *undifferentiated* 42 controls	drawings. Mach-IV. SAPS, SANS, BPRS, IQ (SPMR).	ToM tasks showed a more cynical and pragmatic view of life as indicated by higher scores on the Mach-IV scale. Patients with negative symptoms were less strategic in their thinking than patients with patients with positive symptoms.
(27) Abu-Akel and Abushua'leh (2004)	24 paranoid schizophrenia: *12 violent* 12:0 31.3 *12 nonviolent* 12:0 41.2	12 ToM tasks: 4 sets of 3 tasks: first order ToM task second order ToM task faux pas task Questions asked requiring mental state or empathetic inferencing. BPRS.	Violent patient group had more difficulty on tasks involving empathetic inferencing than the non violent patients, but had better abilities on the tasks involving cognitive-mental states in others.
(121) Gambini *et al.*, (2004)	30 schizophrenia 20:10 40.0 (*paranoid*)	Insight tested by interviewing patients about their delusions. Question pertaining to patients delusions was designed to test whether the shift from a first to a third person perspective could modify the patient's awareness about their delusions.	All 30 patients initially lacked insight but when the perspective changed from the first person to the third person, 7 patients gained insight. Results suggest that in some delusional patients it may be possible to gain access to and modify their mental states.
(32) Greig *et al.*, (2004)	128 schizophrenia: 102:26 62 *paranoid* 5 *undifferentiated* 12 *disorganized* 8 *residual* 41 *schizoaffective*	Hinting Task Continous Performance Task (CPT) Gorham's proverb's test Hopkins verbal learning test WAIS Trail Making Wisconsin card sorting task.	ToM performance differed significantly by schizophrenia diagnosis, with the disorganized group the most impaired relative to the other groups, who did not differ significantly from each other. ToM performance was also significantly correlated with measures of thought disorder and verbal memory. No link of ToM impairment to paranoia. Results suggest ToM variance within schizophrenia population.
(122) McCabe *et al.*, (2004)	35 schizophrenia: 20:15	CBT conversational encounters between chronic schizophrenia individuals and health professionals	Schizophrenic individuals demonstrated intact ToM skills in

		were analyzed in order to investigate how participants used or failed to use ToM relevant skills in social interaction.	conversational interactions.
(123) Schiffman *et al.*, (2004)	90 children with a schizophrenic parent 93 children with a parent with non-schizophrenia psychosis 82 children with non psychotic parents	Role Taking Task (RTT): perspective taking task.	Children who later developed schizophrenia or a schizophrenia spectrum disorder had lower RTT scores controlling for verbal IQ and age. Results imply that ToM deficits in schizophrenia are trait markers of the disease.
(124) Brune (2005)	23 schizophrenia 18:5 38.8 18 controls 8:10 35.5	Pictures of facial effect. 23 questions based on 6 cartoon picture sequences with a variety of first and second order ToM, deception and false belief questions based on these images. WCST, BADS.	Patients were significantly impaired on all tasks involving executive function, emotion recognition and ToM. Deficits in social perception and cognition could only partially be accounted for by impaired executive function. ToM deficits were linked to duration of illness.
(35) Brune and Bodenstein (2005)	31 schizophrenia 23:8 38.6	German proverb task Executive function tests Verbal intelligence. German MWT WCST.	Patient's ability to correctly interpret proverbs was highly correlated with ToM, executive functioning and intelligence. The ability to interpret such metaphorical speech that is typical of many proverbs crucially depends on schizophrenia patients' ability to infer mental states.
(125) Marjoram *et al.*, (2005)	20 schizophrenia 12:8 39.8 20 matched controls 11:9 39.8	ToM cartoons Physical cartoons (Gallagher et al., 2000). IQ (Quick Test, Ammons & Ammons 1962) Krawiecka (1977) Symptom Assessment Scale.	Schizophrenia group scored significantly worse than the controls in both cartoon conditions, particularly on the ToM cartoons. Could not link presence of positive symptoms to impaired performance in this instance.
(126) Schenkel *et*	42 patients: 25:17 41.7	Hinting task Visual and linguistic context	More impaired ToM was associated with poorer

al., (2005)	23 *schizophrenia* 19 *schizoaffective disorder*	processing. Executive functioning: Hayling sentence completion task Verbal IQ (Shipley Institute of Living Scale; Zachary, 1991) BPRS.	performance on both visual and linguistic context processing measures and higher ratings of disorganization. Findings suggest that in chronic patients, ToM deficits may be the result of context processing impairments.
(127) Zalla *et al.*, (2006)	40 schizophrenia: *Disorganized* 11:11 39.8 *Non-disorganized* 8:10 41.6 Controls 19:21 41.2	40 five-card picture sequences of 5 types: 8 small action stories 8 large action stories 8 Social-script stories 8 ToM stories 8 Physical events. Participants had to organize the 5 cards into the correct sequence as quickly and accurately as possible.	Disorganisation symptoms appeared to be associated with a general sequencing impairment, whilst patients without disorganization symptoms displayed difficulties in ordering sequences requiring subjects to infer mental states in story characters along with a relatively preserved performance in correctly arranging mechanical or behavioral event sequences. These results reveal that only schizophrenic patients without disorganization symptoms show a selective deficit in mentalising abilities whereas disorganization symptoms are associated with a more severe event sequencing impairment probably reflecting basic failures of inferential reasoning.

1.11 Critique of Table 1.2

Table 1.2 summarizes the ToM neuropsychological investigations conducted in individuals with schizophrenia. It can be seen that a lot of studies were not well matched for sex within their clinical groups. It is often harder to recruit clinical participants than healthy individuals due to smaller populations from which to recruit

and not everyone with a psychiatric disorder will be willing or able to volunteer to participate in a study.

Some studies were published with absent demographic details such as mean age and sex values were missing from the published paper, although it is unclear whether this is due to the journal article format (i.e. a letter to the editor or a brief communication) rather than the fault of the authors.

A couple of studies did not have a psychiatric or healthy control group, such that the schizophrenia group was compared to sub divisions of itself based on symptomatology and psychopathology (24,126). The inclusion of a psychiatric control group would have allowed mentalising ability and psychosis diagnosis type to be investigated, whilst the presence of a healthy control group would have shown how different the psychiatric group(s) performance was from normal.

ToM deficits in schizophrenia may be related to domain general impairments, such as intelligence and working memory load, rather than reflecting genuine compromised mental state attribution impairment (118). An example of thorough and extensive neuropsychological investigations are the studies of Langdon et al., (105,113,115), who meticulously investigated other cognitive domains, such as working memory, as well as ToM abilities in their studies. They were able to show that schizophrenia patients groups had executive functioning deficits compared to the control groups, but when this was controlled for, the patients still had mentalising deficits relative to the controls. These researchers took this as evidence for the modularity theory of ToM abilities. Studies that do not include other cognitive measures could be said to have ambiguous results since it will not be clear to what extent any observed compromised performance on the ToM tasks is due to a purely

deficient ToM mechanism or may reflect a dysfunction of other cognitive capacities. Due to the problems with interfering variables, which pose the difficulty of being able to reliably distinguish between compromised information processing capacity, IQ, and a genuine ToM impairment, some study groups have suggested and endeavored to construct novel theory of mind tasks comprising low information processing demands and higher ToM demands (e.g.(99,107,118)).

Some studies used several different ToM tasks whilst others used just one. It is not clear whether the above studies were specific investigations into ToM abilities in individuals with schizophrenia or part of a larger study, of which the ToM investigation was a subsidiary aspect. If there are subtle group differences, then the use of just one ToM task may not show this. Furthermore, different question types that test different levels of mentalising ability will be more effective than just one question or one task type. With the previously mentioned difficulty in recruiting psychiatric participants for clinical research, as much data as possible should be extracted from their time participating in the study. Some studies could therefore have benefited from the inclusion of more tasks. An example of this is the Gambini study (121) in which patients' insight about their delusions was tested. A single question was asked in which there was a shift from a first to a third person perspective regarding their delusions. All 30 patients initially lacked insight but when there was this perspective change from the first to the third person, 7 patients gained insight. The authors concluded that in some delusional patients it may be possible to gain access and modify their mental states on the basis of this question. This study investigated self ToM abilities, however, by incorporating a short false belief story or a shortened version of the Hinting task at the expense of several

minutes of time; they could have ascertained how these patients' mental state attribution of other people was affected as well. This would have increased their data by twofold and made the study more interesting in that both self and others ToM attribution would have been investigated.

This issue of a balanced study both for tasks and participants has lead one reviewer of the schizophrenia ToM literature to suggest that more sophisticated ToM tests should include comprehension of multiple ToM picture stories, understanding of proverbs that combine metaphor and mental state attribution, and strategic social thinking (Machiavellian Intelligence) controlling for IQ, psychopathology, and taking into account the onset and the duration of disorder (118).

1.12 Evidence for Frith's positive symptoms theory

Frith's (53) metarepresentation theory implies that compromised function in schizophrenia represents a temporary 'state', rather than a pre-existing 'trait ' effect. Evidence for this comes from studies in which the schizophrenia group is split into sub groups based on the presence (and/or symptom subtype) or absence of symptoms. Patients with negative behavioral symptoms (i.e. avolition and social withdrawal) or positive behavioral symptoms (e.g. incoherent or inappropriate speech) performed worse than other different symptomatic groups and healthy controls. Patients with subjective symptoms of passivity (thought insertion and delusions of alien control) performed relatively normally (e.g.(33,98-100,107,112,116)). Paranoid patients have been shown to exhibit both ToM deficits and no such deficits and it is currently unclear as to the nature of compromised mentalising abilities in such individuals.

1.12.1 Remission studies

Further evidence for a state effect can be observed from remission studies. A group of schizophrenia patients can be tested when psychotic and tested later when they are in remission and are deemed to be well and asymptomatic. Alternatively, rather than testing the same group of patients when psychotic and then have to wait until they are asymptomatic; the performance of a symptomatic schizophrenia group can be compared to that of a remission group. Drury et al., (107) tested 14 schizophrenia patients during an acute phase and during remission and compared them to a psychotic control group and a depressed group. They observed that the schizophrenia group performed significantly worse than the non schizophrenia patients on ToM tasks during an acute phase. There was no significant group difference on the tasks at recovery. This finding provided evidence for the state effect as there was remediation in performance on the ToM tasks when the schizophrenia group was asymptomatic. Furthermore, the paranoid group with persecutory delusions performed poorly on memory tasks during acute phase and on the second order false belief task in the remission phase. This suggests that the observed theory of mind group differences were not necessarily related to the presence of persecutory delusions and the possible interference of ToM abilities with both attention and memory load.

Not all studies that have incorporated a remission group into their paradigm have found unimpaired or normal performance in the remission group, as would be expected according to the state theory of impaired mentalising abilities. Herold et al., (114) using a well balanced ToM task battery task comprised of first and second order false belief stories, a metaphor and an irony task, found that their remitted

schizophrenia group performed significantly worse than the control group on the irony task. The authors took this to be evidence for a trait effect. However, the state effect hypothesis could also explain this. If compromised ToM ability is a state variable at the beginning of the illness (present during an acute episode, absent at recovery), the plasticity of this on-off process may decrease with each relapse (107). This proposal could explain why some studies find patients in remission performing as well as controls and other studies finding a significant difference between these groups. A remission group comprised of patients with a longer duration of illness and hence greater number of psychotic episodes could therefore perform differently to that of individuals with shorter illness duration and less consequent psychotic episodes.

1.12.2 Trait Theory

In direct contrast to this 'state' view is the 'trait' theory in which the ToM deficits in schizophrenia are stable traits. There are several studies that support this view.

Herold et al., (114) reported a schizophrenia group that had compromised ToM abilities in both a psychotic episode and a period of remission. This is in contrast to other previously mentioned remission studies in which ToM abilities were relatively unimpaired during remission. A study investigating ToM abilities in non-psychotic first degree relatives of individuals with schizophrenia showed that they performed significantly worse than controls (119). In an investigation into mentalising and schizotypy, Langdon and Coltheart (128) provided evidence for an association between ToM deficits and schizoptypal qualities among non-psychotic individuals. They found that people with a "high schizotypal" score did less well than their "low

schizotypal" counterparts. If one considers a continuum from normalcy to psychosis, with schizoid personality and schizotypy lying somewhere in-between, then this finding is in agreement with a trait effect for compromised ToM abilities (24).

1.12.3 Evidence for Hardy-Baylé's disorganization hypothesis

A number of studies in the above table have shown ToM task impairment in patients with pronounced thought and language disorganization which provides support for Hardy-Baylé's model (32,101-103,126). According to this model, patients without such language and thought disorganization should be relatively unimpaired on ToM tasks and this is not the case (e.g.(111,118)) so this model cannot fully explain the observed ToM impairments in schizophrenia.

1.12.4 Corcoran's inductive reasoning theory

A recent theory has been put forward on how ToM judgements are produced by individuals with schizophrenia via analogical reasoning skills. This theory differs from that of Frith's or Hardy-Bayle's in that the compromised mentalising ability arises from a hypothesised domain general impairment rather than specific symptomatology.

Corcoran (34,129-131) proposes a model that attempts to account for socio-cognitive difficulties in schizophrenia. She proposes that people infer other people's mental states by retrieving information from episodic memory and reasoning in a conditional manner about the similarities and differences between the memory and current situation. In this way, when a person attempts to infer another's mental state, they initially refer to autobiographical memory in order to see if any remembered event can inform the ongoing problem solving. Any relevant retrieved collection will then

form a base from which the inference process will proceed. Reasoning processes will then allegedly work upon this memory to render a solution suitable to the current situation by considering the relevant conditional or situational variables at play (34). This theory is in contrast to the modular view of mentalising abilities but has similarities to the simulation theory of these abilities. Support for this theory has been shown by several studies. Corcoran and Frith (33) showed correlations between strength of autobiographical memory retrieval and ToM functioning in individuals with schizophrenia. Corcoran (131) found a substantial correlation between an ambiguous sentence comprehension task that required inductive reasoning skills and Hinting task performance. Finally, Corcoran and Frith (34) compared performance of schizophrenia groups and controls on a thematic selection task, the Hinting task and tests of intellectual functioning and narrative recall. They found evidence for support of the hypothesis that in patients with schizophrenia, judgements about the mental states of others are achieved via the use of analogical reasoning. The necessity of the incorporation of a reasoning task into the study paradigm means that evidence for this theory is limited to these three studies currently.

1.13 Non schizophrenia and autism ToM deficits

Compromised mentalising ability has also been observed in individuals with other psychiatric disorders (such as affective disorder) and brain injury and psychopathology (e.g. dementia, stroke, and trauma). These studies are detailed in Table 1 in the Appendix.

Of particular interest are the studies that have investigated ToM abilities in individuals with bipolar disorder and affective psychoses and found evidence for compromised mentalising ability in these clinical groups (132,133). This implies that

psychotic symptoms per se can have effects on mentalising abilities, regardless of diagnosis. In the Marjoram et al., (133) study in which a schizophrenia and affective group was compared to a healthy control group, the presence of high scores for delusions and hallucinations on the Krawiecka psychiatric assessment scale was related to significantly impaired performance on the Hinting task, regardless of diagnosis. This provided support for Frith's theory of impaired mentalising ability in relation the presence of these positive symptoms. However, other studies in which depressed or affective groups were investigated along with healthy control and schizophrenia groups, did not find significant impairment in these groups (101-103,106,107). Similar to the schizophrenia studies, there are conflicting findings in the remission studies of depressed patients. In the Kerr et al., (132) study, the remitted group performed similarly to the control group whilst in the study of Inoue et al., (134) the remission group of unipolar and bipolar patients was significantly impaired on the ToM task compared to a healthy control group. Possible reasons for this could be differing amounts of illness duration and levels of psychotic symptomatology between these study groups.

According to Brüne and Brüne-Cohrs (24), psychopathology always involves disruptions to either social reasoning or mentalising abilities, but the manifestation of this impairment is diverse. In some developmental disorders, such as autism and perhaps those with chronic negative features schizophrenia, acquisition of ToM abilities is fundamentally retarded (e.g. incorrect ontogeny). In contrast to this, lesion studies show that ToM abilities can be secondarily impaired, such that there is normal development and maintenance of ToM abilities prior to the brain damaging event. Outside this dichotomy lie a variety of psychopathological conditions (such as

personality disorders or 'functional psychoses') of which current knowledge is limited as to whether ToM abilities develop correctly during ontogeny.

1.14 Concluding remarks

ToM is a vital aspect of social cognition that allows people to successfully integrate in today's large and bustling social arena. Impairment in this ability has various social and economic ramifications for the affected individual.

The investigation of compromised ToM ability in schizophrenia is a fairly recent and seemingly fertile region of research. Although attention deficits, executive dysfunction and lower IQ scores negatively influence performance on ToM tasks, when these potential confounds are controlled for, significant differences are still observed between schizophrenia groups and healthy controls. Impaired ToM abilities may also relate to poor pragmatic use of language amongst individuals with schizophrenia (104,118). There is a substantial body of evidence that ToM deficits in schizophrenia are likely to be specific rather than to be the result of general cognitive impairments (e.g.(112,113)) see also (23,118), for a detailed overview) and this is in fitting with the modular hypothesis of ToM. There is empirical support for both Frith's and Hardy-Baylé's proposed models for ToM impairment in schizophrenia, with slightly more studies finding support for that of Frith. However, both these models do not fully explain all of the impairments viewed within the various symptom subgroups.

The next stage in research into this observed impairment is the investigation of the neural correlates of mentalising abilities. This being the identification of the brain

regions involved in this skill through the use of imaging techniques and paradigms, which shall be discussed in later chapters of this thesis.

2 ToM neuropsychological investigation

2.1 Aim

The aim of this study was to test the recruited participants on a concise neuropsychological battery of two ToM tasks and a self-monitoring task. It was hoped that these tasks would be sensitive enough to investigate whether any observed group differences were due to state or trait effects, more specifically, current and past positive symptomatology or being at enhanced risk of schizophrenia. For this reason, a self-monitoring task was included as previous studies have shown a significant association between the presence of positive psychotic symptoms and self-monitoring deficits.

2.2 Background

2.2.1 The Edinburgh High Risk Study

All the participants investigated in this study belonged to the Edinburgh High Risk Study (78,135,136). Conceived and managed by Professor Johnstone, the EHRS is a longitudinal investigation into individuals at enhanced risk of schizophrenia. The study began in 1994 and was funded by the Medical Research Council. The sample is drawn from a range of families with enhanced liability to schizophrenia and established Scottish descent. Subjects were recruited based purely on having two or more first or second degree relatives with the disorder, and were not selected based on emerging symptomatology. These individuals are studied serially in comparison with matched healthy controls on a variety of neuropsychological tests, clinical assessments (PSE (137)) and both sMRI and fMRI. The study is currently one of the

largest prospective imaging studies to date. The design of the study differs from other high risk research since subjects are recruited in early adult life (i.e. over the time period of greatest risk of developing the disorder) to address the difficulties seen in follow-up studies such as high attrition rates and the superceding of both data collection and analysis techniques. The study aimed to follow and identify individuals who became ill over the time of their participation in the study such that it would be possible to predict those individuals who subsequently become unwell. This was implemented via serial assessment of neuropsychological test performance, brain structure and function and clinical interview every 18-24 months. Ten to fifteen percent of the high risk group were predicted to develop schizophrenia by the age of 30 years on the basis of the known frequency of schizophrenia in individuals with this degree of heredity, and the actual occurrence of schizophrenia by this age (138). This prediction was proved correct with 21 individuals out of the original 162 high risk participants developing schizophrenia over the course of the study.

2.2.2 Major findings

The high risk participants presented more symptomatology than controls at clinical interview with isolated psychotic symptoms occurring in 2-3 times as many subjects as were expected to develop schizophrenia. In those subjects who went on to develop schizophrenia, the florid condition was preceded by isolated psychotic symptoms in approximately 70% of cases (138-140).

High risk subjects performed worse than controls on intellectual function, executive function, mental control/encoding and learning and memory. However, after

controlling for IQ, only the significant differences on executive function remained (141,142).

Structural imaging found evidence for reduced amgydala-hippocampal complex, thalamus and prefrontal lobe volume (143,144); as well as reduced grey matter density of medial temporal regions and bilateral anterior cingulate compared to controls (145).

Functional imaging showed abnormalities in activation and connectivity in prefrontal-thalamic-cerebellar and prefrontal-parietal regions (139,140). Genetic analysis has shown that the presence of the COMT Val allele is associated with an increased risk of schizophrenia in this already enhanced risk population and its presence was shown to have demonstrable effects on prefrontal brain structure and function (146). These findings imply that high risk relatives inherit a state of heightened vulnerability for the disease.

The overall aim of longitudinal studies, such as the EHRS, is to be a able to pinpoint those individuals who are going to develop schizophrenia (via serial assessments of psychiatric interviews, neuropsychological investigations and both structural and functional MRI) and to be able to intervene in some as of yet unspecified way (e.g.(147)) such that psychosis can be avoided or limited.

2.3 ToM abilities in unaffected relatives

Investigations into ToM abilities and relatives of subjects with schizophrenia are very limited in number and their findings have been inconsistent. Janssen et al., (119) tested a group of 43 individuals with schizophrenia or schizoaffective disorder, 41 first degree non-psychotic relatives and 43 matched controls. Using two ToM tasks, a

first order ToM story and the Hinting task (98), the authors found significant association between liability to schizophrenia and failure on the hinting task, but not the ToM story task, with the relatives having an intermediate performance between the schizophrenic subjects and the controls. The authors concluded that changes in ToM ability were associated with liability to schizophrenia. Alternatively, Keleman et al., (148) using the Eyes Test (149) compared 40 healthy controls against two groups of first degree relatives of schizophrenia patients, an affected group of 14 (individuals with a mixture of psychoses) and an unaffected group of 65 individuals. They found that the affected relative group performed significantly worse on the task than the controls whereas the unaffected relatives showed an intact performance. From this they concluded that the observed ToM deficits were not associated with liability to schizophrenia.

In a study involving high risk children, Schiffman et al., (123) tested 90 children with a parent with schizophrenia, 93 children with a parent with non-schizophrenia psychosis and 82 children with non psychotic parents on a perspective taking task. It was found that controlling for age and IQ, children who later went on to develop schizophrenia or a schizophrenia spectrum disorder had lower scores. The authors interpreted this as evidence for ToM deficits in schizophrenia being trait markers for the disease.

It has been shown that unaffected family members share many of the neurobiological abnormalities found in affected individuals (albeit to a lesser degree) and some of these abnormalities are positively associated with the genetic proximity to an affected relative (e.g.(139,146)). If clinical features (in this case impairment of ToM ability) similar to those occurring in subjects with schizophrenia can be demonstrated

in unaffected genetically related individuals then these may be considered as putative endophenotypic markers of schizophrenia (150).

Using a small battery of two ToM tests and a self-monitoring task, we hypothesised that the ever symptomatic relatives (HR+) would show ToM deficits compared to the controls and relatives who had never experienced psychotic symptoms (HR-). Furthermore, in a secondary analysis, we divided the HR+ group into those who were symptomatic in the past month as revealed by the PSE (HR+Now), or not (HR+Ever), and compared these two groups against each other and a group of high risk relatives who had themselves developed schizophrenia (HRill). It was hypothesised here that those relatives who had been recently symptomatic would perform worse than asymptomatic relatives and similarly to the HRill group, who in turn would perform even less well.

2.4 Self-monitoring

Source monitoring is a term used to describe the cognitive processes involved in determining the source of memory information (151,152). Self-monitoring is an aspect of this phenomenon and can be simply defined as the ability to distinguish between two internal sources (152). It can be further defined as the ability to distinguish the consequences of self-generated actions or thoughts from those of other-generated actions or thoughts. The ability to recognize oneself as the agent of a behaviour (the sense of agency) is the way by which the self builds an entity independent from the external world. Self-recognition is a prerequisite for attributing a behaviour to its proper agent (be it oneself or another person) and ultimately for establishing social communication with our conspecifics (153). Unimpaired self-

monitoring abilities combined with unimpaired ToM capabilities are therefore necessary for successful initiation and maintenance of social interactions, a prerequisite for successful participation in society.

Several information sources are believed to contribute to self-recognition, these being the matching of visual, tactile and proprioceptive signals originating from the same body parts, which contribute to an intermodal sensory image of the body. There is also the matching of one's intentions and the bodily effects of self-generated actions which contribute to the sense of the self as an agent (153).

Currently, there are two main empirically-based hypotheses of action recognition. The central monitoring hypothesis relies on the idea that executed actions generate signals which are centrally monitored and compared, such that action recognition arises as an outcome of this comparison (e.g. (53)). The simulation hypothesis relies on the idea that actions, whether or not they come to execution, are centrally simulated by the neural network, and that this simulation is the basis for action recognition and attribution. Self-monitoring in healthy subjects may be based on a central process that determines deviations between the predicted and observed consequences of physical or mental actions (154). When the predicted and observed consequences match, the observed consequences are experienced as self-generated. Frith and colleagues (155,156) further assume that the future consequences of actions are predicted on the basis of an efference copy of each motor program that is issued (although this is a matter of debate, see (87)). Others postulate that self-monitoring is normally based on a more direct comparison between the intention underlying an action and its observed outcome (e.g. (153)).

2.4.1 Self-monitoring deficits and psychosis

It has been suggested that psychosis is due to deficits in self-monitoring (157-159). The phenomenon of psychosis in schizophrenia consists of bizarre delusions (particularly delusions of control) and hallucinations (most commonly those of an auditory nature). Frith (53) has suggested that these abnormal experiences are a result of a lack of awareness of intended actions, and this may cause thoughts or actions to become isolated from the sense of will normally associated with them. It has been found that schizophrenia patients suffering from these symptom types have impaired self-monitoring (e.g. (160-165). Furthermore, it is assumed from these findings that self-monitoring is mainly impaired in patients with psychosis but hardly in non-psychotic patients. These and similar papers are summarised in Table 2 in the Appendix.

2.4.2 Self-monitoring in High Risk relatives

This study is not the first time that self-monitoring abilities in relatives of patients with psychosis has been investigated. Krabbendam et al., (166) used an action-investigation paradigm to investigate action monitoring in psychosis. A group of patients with a lifetime history of non-affective psychosis (n=37), a group of first degree relatives of patients with non-affective psychosis (n=41), and a group of subjects scoring high on the positive dimension of psychosis-proneness measure by the CAPE (n=40) were compared against control subjects (n=49) scoring in the average range on the positive dimension of the CAPE. In an action monitoring paradigm, subjects had to decide whether the movement they saw was similar to the movement they had made. Patients made significantly more errors on trials with

temporal delays, these were associated with delusional ideation and the strength of the association increased with increasing levels of delusional ideation. Number of errors on all trials was associated with psychosis risk, with subjects with high levels of psychotic experiences and first-degree relatives having intermediate values between patients and controls. The authors concluded that the findings support the idea that an impairment of self-monitoring is part of the liability to psychosis.

2.5 Materials and Methods

2.5.1 Participant Clinical assessment

Around the time of the scan all participants underwent a structured psychiatric interview to identify any psychotic symptoms (the Present State Examination, PSE, (137)). A simple scoring system (138) was administered by two experienced clinicians (Professors Johnstone and Owens). A score of 4 was assigned for definite schizophrenia based on the PSE, and a clinical diagnosis of schizophrenia in terms of the ICD-10 (167). A score of 3 was assigned for any fully rated psychotic feature from PSE items 55-92 (including thought reading, echo broadcast; auditory, visual or other hallucinations; delusions of control, misinterpretation, reference, persecution, grandiosity, influence or other) and from PSE items 128-9 and 135-7 (blunted effect, incongruous effect, neologisms or idiosyncratic use of words, incoherence of speech, flight of ideas). A score of 2 was assigned if any of the features of 3 were partially held or present to a mild degree, plus items 49-54 (perceptual disorders other than hallucinations) and behavioural items 108-9, 118,

and 125-6 (self neglect, bizarre appearance , behaves as if hallucinated, suspicious, perplexed) fully rated, and items 133 (muteness) partially or fully rated.

In essence:

4=schizophrenia

3=fully rated psychotic symptoms

2=partially rated psychotic symptoms

1=fully or partially rated non-psychotic symptoms

0=no symptoms.

For the purposes of this study participants were classified according to the presence of psychotic symptoms. Those with fully or partially held (2/3) psychotic symptoms were classified as HR+, whilst those with an absence of psychotic symptoms (scores 0/1) were classified as HR-. An individual scoring 4 was deemed to be schizophrenic.

2.5.2 Participants

Forty three age and IQ matched individuals from the EHRS were recruited. 25 participants were high risk in that they had two or more first or second degree relatives with schizophrenia whilst 13 controls had no family history of the disease. The high risk group was split on the basis of the PSE into the following groups:

HR+ (n=12): individuals who had reported isolated or transient psychotic symptoms at PSE interview on at least one occasion during the 10 year course of the study.

HR- (n=13): individuals who had never reported any psychotic or partially psychotic symptoms on any PSE interview.

For the secondary analysis the HR+ group was then further split into the following two groups based on past or present psychotic symptoms:

HR+Ever (n=6): individuals who had reported transient psychotic symptoms in a previous PSE interview but not in this one.

HR+now (n=6): individuals who reported isolated or transient psychotic symptoms, usually delusions or hallucinations, within the previous month, at the PSE on the day of testing. This distinction allowed us to differentiate the effects of a general liability to symptoms from their actual effects on testing, and to compare these groups with a sub group of five individuals with schizophrenia (HRill n=5) who had started in the EHRS and had gone on to develop an ICD-10 (167) diagnosis of schizophrenia. Of these, 3 were on medication at the time of testing, whilst one of the drug free individuals had never taken antipsychotic medication and the other had during a brief hospital admission 3 years previously and had been medication free since. None of the other high risk subjects had ever been medicated.

Participants were assigned to either HR- or HR+ group on this basis. Once a person reported an isolated psychotic symptom they remained HR+ regardless of whether they never reported such symptoms again. HR- individuals could become HR+ if at any consequent PSE interview they reported such symptoms.

IQ was estimated via the National Adult Reading Test (6).

The participant demographics are detailed in Table 2.1.

Table 2.1 Participant demographics

Group	***n (m:f)***	***Age***	***NART IQ***
Analysis 1			
HR-	13 (8:5)	30.8 (2.0)	101.4 (8.5)
HR+	12 (5:7)	28.9 (3.7)	101.1 (9.3)
Control	13 (8:5)	29.6 (1.6)	106.8 (7.8)
Analysis 2			
HR+Ever	6 (1:5)	29.2 (3.8)	107 (5.83)
HR+now	6 (4:2)	28.7 (8.4)	95.2 (8.42)
HRill	5 (1:5)	26.8 (4.3)	102.2 (13.4)

Where possible the PSE was conducted on the same day as the scan and the neuropsychological testing. Where this was not possible (e.g. work commitments, difficulties co-ordinating scanner slots) they were conducted as near in time as possible. Since the PSE assessment covers symptoms within the previous month, these small delays were not considered a major issue. Most scans and PSE's were carried out on the same day and were never more than a week apart.

2.6 Tasks

ToM and self-monitoring ability was assessed via a battery of the following three tasks: the Hinting Task, cartoon picture sequences and a self-monitoring drawing task.

2.6.1 Hinting Task

Using the original Hinting Task (98) as a template, we successfully devised and implemented an additional version (see (133)) which was found to be significantly harder than the 10 Corcoran devised scenarios, reducing the chance of a possible ceiling effect in controls. In our previous study, the original 10 Corcoran et al., (98) devised hints gave a mean score of 18.3, whilst the newly devised hints gave a mean score of 16.8, this difference being highly significant, $P<0.005$. The task is designed to test the ability of individuals to infer the real intentions behind indirect speech utterances. There are 10 short scenarios always involving 2 characters. All scenarios ended with one of the characters dropping an obvious hint. The participant was asked what the character really meant when he/she said this. An appropriate response here was given a score of two and the next scenario read out. If the participant gave an incorrect response then an even more obvious hint was added to the story. The

participants were then asked what the character wants the other one to do. A correct response here was given a score of one. If the participant failed again to give a correct response, a score of zero was given for that particular scenario. All Hinting items were read aloud to the subjects, and were repeated as required, to ensure adequate encoding of the information presented and overcome the poor prose recall associated with schizophrenia (168) and potentially present in relatives (169). Furthermore, in order to reduce the potential memory load of the task, a sheet containing all the tasks was placed in front of the subjects for them to read if they so desired. A maximum score of 20 could be obtained. The 10 scenarios can be viewed in the Appendix.

2.6.2 Cartoon picture sequences

The 4 picture sequence ToM cartoons were originally designed and implemented by Martin Brüne (35,118). We used 3 cartoons in a modified version of this task. They represented a ToM scenario involving mutual cooperation and deception of two characters while cheating and deceiving a third character. There were 4 pictures to each scenario and there was an accompanying set of questions relevant to each scenario that tested the participants' ability to appreciate the mental states of the characters involved according to different levels of complexity in the following categories: first and second order false beliefs, reality, deception, cheating, cheating deception and reciprocity. There were four questions for each cartoon giving a maximum total of 12. All testing took place in a quiet distraction free room. The three cartoons and their accompanying questions can be viewed in the Appendix.

2.6.3 Self-monitoring task

The self-monitoring task was a modified version of that initially devised and employed by Mlakar et al., (161) and revised and extended by Stirling et al., (163,170). It was in two parts, in each part the participant had to generate drawings of simple designs and subsequently 'identify' their own drawings (from drawings of the same design by other people) in a recognition paradigm. In test 1, participants selected their own designs and drew out-of-sight. In test 2, the designs were chosen by the experimenter and the participant was able to produce the drawings in full view. Test 1 specifically tests self-monitoring mechanisms along with some recognition memory, whereas test 2 just tests recognition memory.

The specific details were as follows:

Test 1: self-selected drawing, no feedback.

Subjects viewed an A4 card with 24 black ink simple line drawings (e.g. overlapping circles, an asymmetrical triangle etc). They were asked to choose one and draw a similar design on a square paper foil ($12cm^2$) located out of sight underneath an angled screen. Immediately after each trial, the subject's drawing, along with four other foils of the same pattern image previously drawn by other respondents, was presented to the participant on a display board divided into five framed sections, and the participant tried to identify his/her drawing from the five on display, guessing if necessary. After each trial, the participant chose another pattern from the remaining drawings and repeated the procedure as before.

Test 2: experimenter selected drawing, with feedback.

This test employed the same procedure as test 1 except that the participants were able to watch themselves draw each of the selected patterns. This test provided a 'control'

measure of recognition memory in that participants had visual feedback of their own drawings. There were no practise trials and in the first test ten patterns had to be drawn, whilst five were drawn in the second 'control' test, giving a total of fifteen trials in all. Participants' drawings were scrutinised for deliberate markings and fair representation of the original drawing. Any failing these criteria were excluded and a new pattern had to be used. On each trial, suitable foils were selected by the investigator (D.M.) as being clearly compatible with the participant's own drawing. There was a possible score of 10 for Test 1 and a possible score of 5 for Test 2 giving a combined maximum score of 15.

2.7 Statistical Analysis

Data analysis was carried out using SPSS for Windows Version 12.0.

Continuous outcome variables measuring ToM were generated. One-way analyses of variance were conducted to investigate possible differences in age, IQ and sex. General Linear Model (GLM) univariate analysis of variance and planned comparison analysis was conducted investigating group differences on the task totals and sub totals. Groups were defined by the criteria described above in the first instance, (then for the second analysis the HR+ was split into two subgroups, HR+Now and HR+Ever respectively and the HRill group was added).

The total cartoon scores were further divided into seven scores for the above mentioned question types and these were then analysed via GLM univariate analysis of variance and planned comparison analysis.

Due to unforeseen circumstances, one of the HRill was unable to undertake the self-monitoring drawing task so the HRill scores for this task therefore represent the data of four rather than five individuals.

2.8 Results

One way analysis of variance showed no significant difference between the groups for age, IQ and sex. However, there was a trend to significance for IQ (P=0.075) and results are therefore presented both before and after covarying for IQ in the analyses. The individual group scores and descriptives are shown in Table 2.2.

2.8.1 Analysis 1: Symptoms ever or never

In the first analysis, where HR+ and HR- were compared to each other and the control group, GLM univariate analysis, co-varying for IQ, produced no significant group differences in performance on the Hinting Task, self-monitoring task (both for the feedback and no feedback condition subtotals and these combined task totals) and the cartoon sequences overall total score (all P>0.05).

The cartoon sequences were then divided into the different cartoon subtotals and the seven different question types of first and second order false beliefs, reality, deception, cheating, cheating detection and reciprocity questions. Significant group differences were observed for cartoons 2 and 3 and the questions of cheating and cheating detection, as detailed in Table 2.3. Performance was worse for those with symptoms both before and after co-varying for IQ.

2.8.2 Analysis 2: Symptoms in the past, now or ill

The HR+ group was split into those who had reported psychotic symptoms within the past month at the PSE on the day of testing (HR+Now) and those who had

reported transient psychotic symptoms in a previous PSE but not this one (HR+Ever). These were then compared to the HRill.

GLM univariate analysis and planned comparison analyses produced no significant group differences in performance on the Hinting Task and the self-monitoring non-feedback condition. There was, however, a significant difference between the HR+Now and HR+Ever groups on both the self-monitoring control condition and the self-monitoring total (P= 0.024 and P=0.034 respectively). These findings are detailed in Table 2.4.

Table 2.2 Group task scores and descriptives

	HR-	***HR+***	***Controls***	***HR+Now***	***HR+Ever***	***HRill***
Hinting						
Mean	18	18.9	19.1	19	18.8	19.2
SD	2.1	0.9	1.3	0.9	0.9	1.3
Min	14	17	16	18	17	17
Max	20	20	20	20	20	20
Brune Cartoons						
Mean	10.2	9.8	10.2	10.2	9.5	9.6
SD	1.5	1.7	1.3	1.7	1.8	1.5
Min	6	7	8	8	7	7
Max	12	12	12	12	12	11
SM no feedback						
Mean	6	5.3	5.8	4.2	6.3	4.8
SD	2.1	2.2	1.6	2.4	1.4	2.1
Min	3	1	2	1	4	3
Max	9	8	8	8	8	7
SM feedback						
Mean	4.6	4.8	4.9	4.5	5.0	5.0
SD	0.7	0.5	0.3	0.5	0	0
Min	3	4	4	4	5	5
Max	5	5	5	5	5	5
SM Total						
Mean	10.6	10	10.7	8.7	11.3	9.8
SD	2.5	2.3	1.8	2.3	1.4	2.1
Min	7	7	7	5	9	8
Max	14	13	13	12	13	12

Table 2.3 Significant between group differences for Brüne Cartoon Analysis

Task	*P* (IQ Cov'd)	*F*	*P* (no IQ)	*t*	*Between-group contrasts*
Planned Comparison					
Brune Cartoon 2			0.031	-2.248	HR+<HR-&Con
			0.027	-2.313	HR+<Con
Brune Cartoon 3			0.016	2.520	HR+<HR-&Con
			0.028	2.366	HR+<HR-
Cheating			0.034	-2.209	HR+<Con
Reciprocity			0.016	2.520	HR+<HR-&Con
			0.021	2.413	HR+<HR-
GLM univariate analysis					
Brune Cartoon 2	0.049	2.284			HR+<Con
Brune Cartoon 3	0.019	3.815			HR+<HR-
	0.027	3.815			HR+<Con
Cheating	0.044	2.275			HR+<Con
Reciprocity	0.019	3.815			HR+<HR-
	0.027	3.815			HR+<Con

Table 2.4 GLM significant findings for analysis 2

Task	*P* (IQ Cov'd)	*F*	*P* (no IQ)	*F*	*Significant between-group differences*
Analysis 1					
Brüne Cartoons	0.808	0.214	0.787	0.241	None
Hinting	0.240	1.487	0.170	1.863	None
SM no feedback	0.531	0.645	0.620	0.484	None
SM control	0.414	0.906	0.282	1.312	None
SM combined	0.728	0.320	0.693	0.370	None
Analysis 2					
Brüne Cartoons	0.679	0.398	0.767	0.270	None
Hinting	0.827	0.193	0.850	0.164	None
SM no feedback	0.440	0.881	0.190	1.894	None
SM control	0.053	3.795	0.043	4.063	HR+Now<HR+Ever P=0.024, t =-2.550
SM combined	0.404	0.978	0.095	2.831	HR+Now<HR+Ever P=0.034 t =-2.369

2.9 Discussion

In this study we sought to investigate whether individuals at enhanced risk of schizophrenia showed impairment of their ToM and self-monitoring capabilities as

compared with well controls. In the large study (EHRS, (78,136)) from which the participants were drawn, it was found that many more subjects than are likely to develop schizophrenia showed similar (if lesser) cognitive impairments to sufferers from the psychosis. These were more marked in those who had transient or partial psychotic symptoms than in those who did not. For this reason we hypothesised that those who had transient or partial psychotic symptoms (HR+) would have more impairment of ToM capabilities than those not so affected. Two tests of ToM were used - the Hinting task and cartoon picture sequences along with a self-monitoring drawing task and there were two analyses. In the first analysis, high risk subjects who had had transient or partial psychotic symptoms (HR+) were compared to those who had not (HR-) and controls. As far as the Hinting task was concerned no significant differences were shown. This is in direct contrast to the study of Janssen et al., (2003) who found a significant association between schizophrenia risk and failure on this task (119). There were also no significant group differences on the self-monitoring task. The cartoon picture sequences did show a number of differences in agreement with the hypotheses (Table 2.3). It probably is the most sensitive of the three tests used and it may be that the lack of difference shown in the other tests is due to the small number used. The battery of ToM tasks was well balanced in that it incorporated both verbal and pictorial paradigms and tested various levels of ToM ability.

The second analysis divided the HR+ group into two: a) those who reported transient or partial psychotic symptoms at or around the time of the PSE carried out at the ToM testing (HR+Now) and b) those who reported transient or partial psychotic symptoms in a previous PSE but not at the time of the ToM testing (HR+Ever). This

was done with a view to addressing the role of current symptomatology and impairment of ToM. These two HR+ groups were compared to a group of subjects from the EHRS who had gone on to develop schizophrenia. The high risk subjects with current symptoms performed less well on the self-monitoring task than those who said transient or partial psychotic symptoms had occurred on another occasion. As well as a significant between group difference on the self-monitoring combined total, the HR+Now also performed significantly worse than the HR+Ever on the control aspect of the task. This is an interesting finding as it would be expected that a difference would be observed in the non-feedback rather than the feedback condition. This finding could be due to the low group numbers in this particular analysis. None of these individuals had ever had antipsychotic treatment at that time and although the HR+Now described symptoms when directly asked at PSE, they didn't see these symptoms as incapacitating and most of them remained high functioning. At superficial contact these young people would not have appeared impaired in any way and yet their ToM and self-monitoring capabilities were restricted.

As mentioned previously, it appears that self-monitoring is mainly impaired in patients with psychosis but hardly in non-psychotic patients. Similarly, previous neuropsychological investigations have found a significant link to the presence of positive psychotic symptoms (delusions and hallucinations) and impaired ToM performance (e.g. (98-100,103,112,133)). The findings from this study are therefore in agreement with the literature and provide evidence for compromised self-monitoring and ToM abilities in HR+ individuals of a state nature.

The previous three studies that involved the drawing of geometric shapes with and without feedback, found impaired self-monitoring abilities in their schizophrenia

groups. Mlakar et al., (161) found that those schizophrenia patients with Schneiderian symptoms were most impaired on the task. Stirling et al., (163) found that schizophrenic individuals with delusions of alien control were the most impaired whilst in their later study (170) impaired performance was related to both the severity and extent of positive symptoms. The two Stirling et al., studies (163,170) and the Krabbendam et al., (166) study, in which the first degree relative group performed intermediately between the impaired patient group and the normal functioning control group, had larger participant numbers than this study.

The HRill group's performance warrants discussion. They had the highest mean score on the Hinting task and on the self-monitoring feedback condition they performed at ceiling, whilst on the non-feedback condition their performance was impaired. This self-monitoring performance is similar to the findings of Turken et al., (171), who found that their schizophrenia group performed seemingly unimpaired on the feedback aspect of the task but had significant difficulty correcting their errors without external feedback.

Our group was particularly small and seemingly high functioning. The medication that three of the five individuals were currently taking could be having positive cognitive effects, such as the documented normalizing of attention (20,80).

As regards the second analysis, we originally hypothesised that the HRill would perform the worst, the HR+Ever the best and the HR+Now would perform similarly to the HRill. This was not the case as it was the HR+ groups which were the most impaired.

The conflicting data in the two previously reported studies of first degree relatives could result from the use of different ToM tasks to this study, with the exception of

the Hinting Task that was used in a shortened Corcoran (98) version (4 instead of 10 scenarios) in the Janssen study. By shortening the Hinting task the sensitivity of it to show group differences will probably be decreased. Keleman et al., (148) only used the Eyes Task in their study. This lack of task uniformity will not only have tested ToM ability to different extents across the experimental subject groups but also may well have made demands on different ToM capabilities.

Furthermore, this study was limited in size, particularly in the second analysis. Both the Janssen and Keleman studies had larger group sizes. With similar group sizes in this particular relatives study, more significant group differences may have been apparent.

Caution needs to be applied interpreting these findings in light of this power issue and similar investigations on these clinical populations but with more substantial group numbers are required. Furthermore, as regards the state and trait issue in relation to risk of schizophrenia, it may not be one or the other but an additive combination of the two. It could be that people with a genetic liability for psychosis are impaired on ToM tests throughout their lives, and this impairment becomes more pronounced during psychotic symptoms.

It is not possible on the basis of these results to fully elucidate whether this is a state or trait effect. The poorer performance of the HR+, the HR+Now performing less well than the HR+Ever on the self-monitoring task and the fact that the HR- did not differ significantly then the control group, would support a state effect, the difference of performance being due to the experience of symptoms at, or at least relatively close to, the time of testing. However, the results of cognitive and psychopathological function in this particular study group as a whole are indicative

of a graded trait effect (136) and such a possibility cannot be excluded within this study.

3 Functional Magnetic Imaging (fMRI)

3.1 Introduction

The relatively recent invention and incorporation into research of functional brain imaging techniques has allowed the in vivo workings of the brain to be observed. These new imaging methods have identified large numbers of functionally-specific areas in the human brain, some of which seem comparable to other species (i.e. primates) and others seemingly unique to humans. Within these latter regions, detailed investigations have helped to reveal the underlying processes. As well as providing insights into function, these techniques have also enabled brain structure to be viewed in ever finer detail. In conjunction with investigations into the function and structure of the brain in alleged healthy individuals, detailed exploration into psychiatric disorders has revealed insights into brain dysfunction and morphology in disorders such as schizophrenia. The ultimate aim of neuroimaging is to be able to improve the spatial and temporal resolution of the concerned imaging techniques such that the internal functioning of the brain (e.g. that during mentalising) can be observed with the greatest clarity in almost real time.

3.2 Imaging techniques

Functional brain imaging is the use of a range of techniques to define the physiological changes that accompany brain activity. Our current understanding of the neural processes underlying brain activity and function are however limited to the current spatial and temporal resolution of these techniques.

Electrophysiological imaging methods are based on direct mapping of transient brain electrical dipoles generated by neuronal depolarization (electroencephalography,

EEG) or the associated magnetic dipoles (magnetoencephalography, MEG) associated by the summation of neuronal electrical events. These two techniques can be used to measure brain electrical activity of either a spontaneous nature or of a synchronous nature in which activity is measured pertaining to specific stimuli and events of interest (event related potentials, ERPs, or event related fields, ERFs). These techniques define the underlying cortical events in real time (10-100 msec) but provide relatively poor spatial resolution of many mm-cm (172-174).

Metabolic and vascular imaging techniques comprise three main techniques.

Single photon emission computerised tomography (SPECT) uses the detection of radionuclide tracers introduced to the blood which emit single gamma-ray photons. These photons interact with a sodium crystal to produce a detectable signal.

Positron emission tomography (PET) also uses radionuclide tracers (e.g. H_20^{15} for regional cerebral blood flow and F^{18} flouro-deoxy-glucose for regional cerebral glucose metabolism), which is injected into the blood stream and diffuses across the blood brain barrier, accumulates and then circulates within the tissue. The tracer then decays and results in the emission of positrons which interact with electrons to produce two separate gamma rays, the detection of which produces the measurable signal (175).

fMRI indirectly measures changes in blood oxygenation due to differing magnetic properties of oxygenated and deoxygenated blood. Unlike the two above techniques that rely on exogenous tracers, it uses an endogenous tracer in the form of the brains blood response to neuronal activity. This technique will be discussed in greater detail below.

The physiological basis of functional imaging methods are generation of an extracellular electrical potential, increased oxidative metabolism (and glucose substrate utilization) and enhanced blood flow and relative oxygenation. fMRI and PET provide information on the increases in blood flow accompanying neuronal activation with relatively high spatial resolution (approximately 1-10mm) but have a temporal resolution limited by the much slower haemodynamic changes that accompany neuronal depolarization (172).

3.3 fMRI

Magnetic resonance arises from the interaction of nuclei which have a magnetic moment with an applied magnetic field. The frequency of the energy emitted by an excited nucleus is proportional to the magnetic field experienced. Blood oxygenation level dependent (BOLD) fMRI uses the imaging contrast which arises as a consequence of the higher ratio of oxy- to deoxyhaemoglobin in local draining venules and veins that accompanies neuronal activation (176). BOLD fMRI images signal contrast arises from changes in the local 'magnetic susceptibility', an index of the extent to which an applied magnetic field is distorted as it interacts with a material. When bound to oxygen, haemoglobin is diamagnetic, while deoxygenated haemoglobin is paramagnetic. Magnetic flux is reduced in diamagnetic materials (i.e. the material exerts little magnetic effect on the surroundings and the applied magnetic field is repelled). In contrast, paramagnetic materials have an increased magnetic flux (i.e. the material has a significant magnetic effect on the surrounding and the applied magnetic field is attracted into the material). In areas of increased neuronal activity, an increase in local blood flow and volume results in an increase in oxygen. A change in haemoglobin oxygenation therefore leads to changes in the

local distortions of a magnetic field applied to it. Increased oxygenation of blood gives rise to increased signal from water both in blood vessels and from the surrounding brain tissue (172,177,178).

3.3.1 BOLD Response

The energy source of the brain is derived mainly from the oxidation of glucose. Blood flow in the brain may be locally increased in order to meet demands for oxygen and glucose supply for action potentials or neuronal inhibition, and is therefore taken as an indication of increased synaptic energy utilization to drive neuronal response. This relationship between the haemodynamic response and neuronal activity is not yet clear and could be more complex than we currently understand it to be (179). The time course of the BOLD response in a region of activation is complex and different parts of the time course may provide distinct information. There is an initial small decrease in signal intensity (the early 'dip') that evolves over the first second following a stimulus. There is then a progressive increase in signal intensity over the next 2-4 s. For a simple stimulus that does not cause physiological habituation, the signal change is maintained at a relatively constant level for the period of stimulation. After the stimulus stops, the BOLD signal decreases over a few seconds to a level below the initial baseline (the 'undershoot'), from which it recovers slowly over a few seconds. Generally, the time from onset to final return of signal intensity to baseline is in the region of 12-18 seconds, even for a brief stimulus. Furthermore, the BOLD response is not spatially very specific to areas of neocortical activation (180,181).

The goal of fMRI analysis is to detect in a robust, sensitive and valid way, those parts of the brain which show increased intensity at the points in time that stimulation was applied. In other words, the aim of fMRI analysis is to identify in which voxels' time series the signal of interest is significantly greater than the noise level.

The correlation between neuronal activation and aspects of cognitive processing is currently investigated in two main types of fMRI paradigms.

3.3.2 Blocked paradigms

These are the most commonly used fMRI experimental protocols and allow for the examination of levels of a category in separate blocks of trials in order to evoke a response to a specific cognitive process of interest. 'Experimental' blocks which have been specifically designed to evoke the cognitive process of interest are flanked by 'control' blocks, which will ideally evoke all cognitive processes except for the process of interest (81). Cognitive subtraction is then undertaken in which the averaged activations from the control condition are subtracted from the averaged activations from the experimental condition. The remaining activations from this process will be allegedly attributed to the cognitive process under investigation. The subtraction process relies on the assumption that all variables except for the variable under investigation have been matched equally and held constant in the different conditions. Blocked procedures allow for considerable experimental flexibility, such as parametric and multi-factorial designs (182). The major advantage of this paradigm is that they convey robust responses to the cognitive process of interest

with neural activity being measured and averaged across a block of trials. It does however have the limitation in that it does not allow for discrete event analysis which can result in participants becoming affected by the predictability of trial presentation (habituation and other effects) in both the experimental and control blocks. This paradigm is not without its critics in that cognitive subtraction relies on the theory of 'pure insertion' which states that a cognitive process of interest can be added to other cognitive processes without impacting on the ensuing responses associated with them. However, without a measure of the original processes both with and without the addition of the process of interest, one cannot be certain that one has extrapolated the responses attributed to the processes independently, or indeed, whether these responses are mediated by the existence of the additional process during the experimental task (81,183).

3.3.3 Event-related paradigms

These paradigms differ from blocked paradigms in that individual trial events are measured rather than a temporally-integrated signal. They allow the presentation of trials in an unpredictable order. In a typical event-related paradigm two separate trial types (e.g. words versus pictures) might be randomly intermixed in quick succession. The separate signal contributions of the two kinds of trial type are then compared directly to each other. These paradigms are possible due to recent technological advances in the speed at which fMRI can be acquired, the fact that even brief periods of neural activity produce measurable signal changes and the heamodynamic response provides a highly consistent response that summates over sequential events in an approximate linear way (182). The majority of studies still use the blocked

design but use of event related design paradigms are in the ascendance. Despite event-related designs having reduced statistical power to detect activation relative to block design they convey valuable advantages. They make it possible to examine the unfolding of sequential processes (e.g. in paradigms with a delay interval interposed between the stimulus and response), they allow trials to be categorized by subjects' performance (e.g. correct versus incorrect trials) and the randomized and unpredictable sequences prevent participants from locking into a mental state (184). There is also the possibility of using both these paradigms in a mixed 'event-related and blocked' design. These mixed designs allow for the distinction between transient and sustained processing (184,185).

3.3.4 Processing of fMRI data

Having obtained the fMRI data, there are several processing stages that need to be implemented before the statistical analyses that will show which brain regions were significantly activated by the concerned task(s) can be implemented.

The raw MR signal is obtained by digitising the demodulated radio frequency signal that is detected by the receiver coil. The raw data is 'k-space' data which is a spatial frequency transformation of real space. Before image analysis can be undertaken the raw 'k-space' data is reconstructed into images that look like brains via a fourier transform and several pre-processing steps need to be implemented.

Slice-timing correction: as each slice in each volume is acquired at slightly different times, and later fMRI analysis assumes that all slices were captured instaneuosly, it is necessary to adjust the data such that it appears that all voxels within one volume have been acquired at exactly the same time.

Motion correction: Head movement in a scanning session will mean that the position of the brain within the functional images will vary over time. This will mean that any particular voxel's time series will not, over time, refer to the same position in the brain. Head motion then has two possible effects, the first being that if the head moves in time with the experimental stimulus then the resulting changes in image intensity may be indistinguishable from a 'true' experimental response. Conversely, if head motion occurs with time divorced from the experimental design, this will generally have the effect of producing changes in image intensities that will appear as an additional source of noise when the experimental effect is later modelled, worsening the signal to noise ratio and making the detection of a response that more difficult. Each volume is consequently transformed (using rotation and translation) so that the image of the brain within each volume is aligned with that in every other volume.

Blurring/smoothing: each volume is spatially blurred to increase the 'signal to noise ratio', this being a measure of how big the signal of interest (the change in image intensity that arises as a result of application of stimulation) is compared with the noise level. The background noise is defined as unavoidable random variations in image intensity which is present even when no stimulation is applied. Some of this background noise is removed by the use of high and low-pass filtering that remove slow and high frequency noise respectively. It is important to choose a filter that removes noise without corrupting the underlying stimulus-related signal.

Intensity normalisation: After smoothing, each volumes overall intensity is adjusted such that all volumes have the same mean intensity.

Registration: this refers to the process of aligning the different brain images from all sessions into some common space or 'standard brain space' such as a study specific template. Templates are the average of many brains all averaged into any common co-ordinate system (186,187).

Once these pre-processing and processing steps have been undertaken the fMRI data can then be statistically analysed in order to investigate the brain region response to the different task stimuli (more specifically, how the stimuli effect the BOLD response). This analysis is implemented via the concerned research team's choice of fMRI analysis software. The statistical analysis will enable brain activations in different task conditions to be investigated. Group analyses are the most common form of analysis in the neuroimaging literature (as opposed to single subject individual analysis) and this is the method used in the fMRI analysis of the task imaged in this thesis. Here, brain images from a dozen (or more, in order to increase statistical power) are combined into a common space as mentioned above. This enables one to view whether an activation pattern is consistent across subjects; enables different subject groups to be compared and contrasted to one another, and can provide greater statistical power than individual subject analyses. The drawback to this approach is the blurring that occurs of activation maps due to imperfect registration across physically different brains. Furthermore, as individuals differ in their functional as well as physical anatomy, more blurring occurs in group-averaged data (188). Another approach is to conduct a region of interest (ROI) analysis, in which study is focused on a particular part or parts of the brain as opposed to the entire brain volume. These can be done on the individual level or on groups.

3.4 ToM imaging studies

Table 3.1 contains examples of relevant ToM neuroimaging studies and has examples of all the neuroimaging techniques mentioned earlier. There are several included examples of studies that use eye gaze tasks, particularly the 'Eyes' task (149). However, in the interest of both relevance and brevity, not all studies that have used such tasks are included, nor are imaging studies of face recognition, facial effect and emotion (an example of such paradigms is however included). Although clearly aspects of social cognition, these facial tasks are not pure ToM tasks in that they do not require understanding of another's mind. Indeed, as regards the 'Eyes' task, it is debateable as to whether this task is an emotion recognition paradigm or an advanced ToM test (as stated by Baron-Cohen in the title of the first publication detailing the task) sensitive to subtle ToM deficits. In order to say one is mentalising, one needs to construct second-order (or meta-) representations in order to represent how another represents the world as being. Although the 'Eyes' task is clearly a social cognition task, as it does require the representation of an agent's attitude (e.g. anxiousness), it does not require the representation of the content of that attitude. Without this representation of both attitude and content, one is not properly representing how another represents the world and consequently this does not amount to metarepresentation. It is the inferring of the content of another's belief and not just inferring that they have a belief that is the crucial test for a theory of mind. In this way, the eyes test is not a test of ToM in this strictest sense, but it may be a ToM measure in the broader sense in that it taps ToM related skills (as eloquently discussed in (189)). With some of these eye and facial recognition studies being left

out, this table could be said not to represent a fully extensive and exhaustive literature search.

As with the neuropsychological investigations, the tasks used in the above imaging studies are of a pictorial and verbal nature. Some tasks have been adapted straight from the neuropsychological literature, such as false belief stories and cartoon picture tasks. Other tasks have been specifically designed for imaging paradigms such as video sequences, games and animations of intent.

Table 3.1: ToM imaging studies

Study	*Population*	*Tasks*	*Activation*
(190) Baron-Cohen *et al.*, (1994) SPECT	12 healthy males.	Deciding if a word is a Mental-related word or not. Deciding if a word is a body-related term or not.	Right orbito-frontal cortex (BA11) relative to decreased activity in the left frontal-polar region (BA10).
(191) Fletcher *et al.*, (1995) PET	6 right-handed males. Mean age 38yrs.	TOM stories Unlinked sentences Physical stories.	Left medial frontal gyrus predominantly BA 8, extending into posterior BA9 and the anterior cingulate cortex. Additional activation in the posterior cingulated cortex and inferior parietal lobe on the right (BA40) in ToM condition relative to other stories.
(192) Goel *et al.*, (1995) PET	9 right handed males.	TOM condition: How would someone with a background knowledge of Christopher Columbus infer the function of an artefact? Baseline condition: visual perception and analysis, simple decision and motor response. Memory retrieval: presentation of modern familiar stimuli. Deciding if the stimuli are used for food preparation or personal care.	Selective activation of the left medial PFC (BA9). Compared with simple inference condition: Left posterior temporal lobe, left anterior temporal lobe and left medial frontal lobe.
(193) Happé *et al.*, (1996) PET	5 Normal controls. 5 Asperger males.	Same as Fletcher et al (1995).	Normal controls: Left medial PFC (BA8) Asperger: No activation of BA8, but an adjacent, more ventral area of left medial PFC (BA left 9/10).

(194) Baron-Cohen *et al.*, (1999) fMRI	6 male normal controls 6 female normal controls. 6 persons with autism. 4 male 2 female	Looking at photographs of eyes and deciding which of two words best described what the person is feeling or thinking. Looking at photographs of eyes and deciding whether it is a man or a woman.	Various activations in controls, comprising :Fronto-temporal neocortical region, comprising left dorsolateral (BA 44,45,46), left medial PFC(BA9); supplementary motor area and bilateral temporo-parietal regions (BA 21,22,39,40) Non-neocortical areas: left amygdala, left hippocampal gyrus (BA27, 30), bilateral insulae and left striatum. In the autism group there was less extensive activation of frontal components and no amygdala activation at all.
(195) Brunet *et al.*, (2000) PET	8 right-handed males. Mean age 23.3 yrs.	Attributing intentions to the characters of a comic strip AI Physical causality cartoons with characters PC-CH. Physical causality cartoons with objects PC-OB.	AI versus PC-CH comparison: Right middle and medial PFC including BA8/9, right inferior prefrontal cortex(BA47), right inferior temporal gyrus(BA20), left superior temporal gyrus(BA38), left cerebellum, bilateral aneterior cingulate(BA24), and the middle temporal gyri(BA21).
(196) Castelli *et al.*, (2000) PET	6 right-handed males. Mean age 24.5 yrs.	Watching computer-presented animations with two shapes and telling what was happening. 3 types: TOM Goal-Directed Random action.	More activity during TOM compared with Random action: Temporo-parietal junction (BA22/39) Basal temporal region(BA37,38) Extrastriate cortex (BA19/18) Medial PFC (BA9). Differences more significant in right hemisphere except for medial prefrontal cortex.
(197) Gallagher *et al.*, (2000) fMRI	5 right-handed males 1 " " female. Mean age 30 yrs.	Stories same as Fletcher et al. (1995) ToM cartoons Non-ToM cartoons jumbled pictures.	TOM Stories: Broader region of the medial PFC extending into BA9 and closely associated with the anterior cingulate region of BA 32. Cartoons: Medial prefrontal cortex, restricted to BA8.
(198) Russell *et al.*, (2000) fMRI	7 Normal male controls. Mean age 40 yrs. 5 male right-handed Schizophrenics. Mean age 36 yrs.	Same as Baron-Cohen et al. (1999)	*Healthy subjects*: Left inferior frontal gyrus reaching into the insula (BA44/45/47) Into the medial frontal lobe (BA45/9), in the left middle (BA21) and left superior temporal gyrus (BA22). *Schizophrenia:* Significantly less activation in the left

			middle/inferior frontal cortex. (BA9/44/45).
(199) Sabbagh and Taylor (2000) ERP	20 4yr olds 20 6yr olds 20 8yr olds.	Mental representation task (belief) Non mental representation task (photographs).	Neural activity elicited by mentalising task compared to non mental reasoning task was characterized by a focally enhanced posivity over left frontal areas which were diminished over left parietal areas.
(200) McCabe *et al.*, (2001) fMRI	Even but unspecified number of healthy controls.	2 person reciprocal exchange tasks for cash rewards: Trust game Punish game Mutual advantage game.	Prefrontal regions were more were more active when participants were playing a human than when they were playing a computer. Exact location of these regions varied from subject to subject.
(48) Vogeley *et al.*, (2001) fMRI	8 right-handed males.	Stories without SELF same as Fletcher et al. (1995) E Only TOM stories E Only SELF stories E TOM and SELF stories C Baseline condition: unrelated sentences C Stories without TOM/SELF, Physical stories.	Activation in TOM: Predominantly in the right anterior cingulate and left temporo-polar complex. Activation in SELF: Right temporoparietal junction and bilaterally anterior cingulate cortex and right premotor and motor cortex and precuneus TOM&SELF Right lateral PFC.
(201) Bertoz *et al.*, (2002) fMRI	12 right handed healthy male volunteers.	Story tasks describing the following situations: Normal behavior Embarrassing situations Violations of social norms.	The stories regarding transgression of social norms involved medial prefrontal, temporal regions, lateral orbitofrontal cortex (BA47) and MPFC. These activations were similar for both intentional and unintentional social norm violation with a tendency to be more pronounced for the unintentional violations.
(202) Calder *et al.*, (2002) PET	9 post menopausal females.	Eye gaze task in which there were 3 conditions with different proportions of eye gaze: 100% direct [0% averted] 50% direct [50% averted] 100% horizontally averted [0% direct] 2 control conditions with faces' gaze averted down or eyes closed.	Contrasts of control conditions revealed medial frontal involvement. Parametric analyses showed a significant linear relationship between increasing proportions of horizontally averted gaze and increased rCBF in the MPF cortex. Increasing proportions of direct gaze was associated with increased rCBF in a number of areas including both the medial and superior temporal gyri.

(203) Castelli *et al.*, (2002) PET	10 individuals with either autism or aspergers. 10 healthy controls.	Same as Castelli *et al.*, (2000) paradigm: Watching computer-presented animations with two triangle shapes and telling what was happening. 3 types: TOM Goal-Directed Random action.	*Controls*: (MPFC [BA9], STS, TPJ and temporal poles). The autism group activated less than the controls in all of these regions. Although extra-striate cortex showed same amount of activation in both groups, in the autism group this region exhibited reduced functional connectivity with the STS at the TPJ region. Authors propose that this suggests a physiological cause for the mentalising dysfunction in autism, this being a bottleneck in the interaction between higher order and lower order perceptual processes.
(204) Blakemore *et al.*, (2002) fMRI	5 right-handed males 5 right-handed females.	Similar protocol to Castelli *et al.*, (2002) triangle paradigm, 2 moving shapes, 5 conditions: Animate-Contingent Animate-Non contingent Inanimate-Contingent Inanimate-Non contingent Baseline	Right middle frontal gyrus Left STS Mid temporal gyrus Right intraparietal sulcus.
(117) Brunet *et al.*, (2003) PET	7 medicated male schizophrenic patients. Mean age 31 yrs. 8 matched healthy male controls. Mean age 23.3 yrs.	Pictorial attribution of intent task 2 matched physical logic tasks, with and without human figures.	Attribution of intent elicited significant right PFC activation in the controls but not in the schizophrenia group. In both groups, perception of human figure elicited bilateral activation of occipitotemporal regions and of the posterior part of the STS.
(205) Calarge *et al.*, (2003) PET	13 healthy volunteers (7 females, 6 males). Mean age 26.5 yrs.	ToM task involved creating a "story" about the mental state of a stranger who they imagined encountering on a park bench. In a control task they read aloud a story involving no mental state attribution.	ToM activated medial frontal cortex (BA32,10), superior frontal cortex (BA 6/9/32), anterior and retrosplenial cingulate and anterior temporal pole, all predominately left sided.
(206) Kampe *et al.*, (2003) fMRI	16 healthy right handed volunteers (8 male, 8 female).	Eye gaze task Name calling task.	These two tasks of different modality and sensory channel, both activated the paracingulate cortex and bilateral temporal poles. Study provides evidence that mentalising is involved in understanding the signals that a sender emits to initiate communication with

			someone.
(207) Saxe and Kanwisher (2003) fMRI	25 right handed healthy volunteers (13 male, 12 female).	4 types of verbal story: false belief mechanical inference human action nonhuman descriptions. In a second study they presented photographs of people and nonhuman objects.	A portion of the TPJ, called TPJ-M by the authors, was found to be specifically involved in reasoning about the contents of another person's mind. This activation was bilateral.
(208) Wicker *et al.*, (2003) PET	10 healthy right handed male volunteers.	Subjects asked to attribute hostile or friendly intentions to video-taped actors who directed attention towards or away from the subjects. Testing attribution of an emotion regardless of gaze direction.	Anterior region of STG was selectively activated during analysis of emotions through eye contact.
(209) Decety *et al.*, (2004) fMRI	12 right handed healthy volunteers (6 male, 6 females).	Subjects played a computer game, according to a set of predefined rules, either in cooperation with or in competition against another person.	Both cooperation and competition activated a common fronto parietal network and anterior insula. Activation in orbitofrontal cortex was specific to cooperation, whilst inferior parietal and medial prefrontal cortices were specific to competition.
(210) Gallagher and Frith (2004) fMRI	12 healthy volunteers (8 male, 4 female). Mean age 35.98 yrs.	Short (3s) videos of actors performing expressive and instrumental gestures. Participants had to either recognize gesture or monitor position of hands.	Different neural networks activated: Perception of expressive gestures activated anterior paracingulate cortex, amygdala, bilateral temporal poles and right STS. Instrumental gestures elicited activation in left-lateralised system previously associated with language and motor imitation.
(211) German *et al.*, (2004) fMRI	16 healthy adult volunteers.	Short 5 second clips of actors performing or pretending to perform (covert conditions, subjects not directed to attend to actors' mental states) everyday actions.	Increased activity in MPFC (BA's 6/9/10/32), inferior frontal gyrus bilaterally (BA 44/47), temporoparietal regions (BA21/22) and parahippocampul areas such as the amygdala, when subjects viewed pretend actions as compared with real ones.
(212) Ishii *et al.*, (2004) MEG	16 healthy adult volunteers (8 male, 8 female).	Emotional video vignettes: Sad Angry Happy Neutral.	Significant activations in bilateral MPFC in alpha frequency band were elicited by happy-sad and angry-sad paired vignettes. Implies

			bilateral MPFC is involved in comprehension of emotional states of others.
(213) Lui *et al.*, (2004) ERP	Healthy volunteers.	Belief judgment task Reality judgment task.	A late ERP component (peaking around 800ms) with left scalpel distribution around possible orbitofrontal cortex differentiated judgements about belief and those about reality. Authors belief this to be associated with decoupling mechanism that distinguishes mental states from reality.
(214) Rilling *et al.*, (2004) fMRI	19 healthy volunteers (11 females, 8 males). Mean age 21.8 yrs.	Ultimatum game Prisoner's dilemma game with both alleged human and computer partners.	ToM regions (such as STS and PFC) activated along with task specific regions. Activations stronger for human rather than computer partners.
(215) Walter *et al.*, (2004) fMRI	13 healthy right handed volunteers (6 males, 6 females). Mean age 25.15 yrs.	Story task: Physical stories Private intention by 1 agent Private intention by 2 agents Communicative intentions.	Anterior paracingulate cortex (PCC) was activated when a represented intention implied social activation and therefore had not yet actually occurred. Authors claimed to have demonstrated that the anterior PCC is not necessarily involved in the understanding of people's intentions per se, but primarily in the understanding of the intentions of people involved in social activation.
(216) den Ouden *et al.*, (2005) fMRI	11 female healthy volunteers.	Factorial intentionality design. 2 factors: Causality (intentional or physical events) Prospective memory (present or absent) In each condition, subjects answered questions about various hypothetical scenarios, which related to either to the link between the subject's own intentions and consequential actions (Intentional causality) or to the link between a natural, physical event and its consequences (Physical causality). Prospective memory task embedded in half of these tasks.	Answering questions about intentional causality versus physical intentional causality activated a network or regions related to mentalising abilities (MPFC, temporal poles, STS). Precuneus was activated more when thinking about intentionality. Activations were observed in the right parietal cortex, precuneus and frontopolar cortex (BA10). Interestingly, different subregions within precuneus and posterior cingulate cortex were activated in both main effects of intentional causality and prospective memory. These two regions appear to subserve thinking about one's own intentions and consequent actions and

			bearing in mind an intention to make an action. Study also found evidence for different regions of mPFC playing different roles in thinking about intentions.
(217) Hymes *et al.*, (2005) fMRI	18 healthy volunteers (9 male, 9 female).	Verbal perspective taking study of 3 conditions: ToM: what characters are thinking Emotional: what characters are feeling Control: details of the story.	Medial prefrontal lobe (BA 11 and 25) was preferentially involved in emotional as well as ToM perspective thinking.
(218) Kim *et al.*, (2005) fMRI	14 healthy controls 7 males 7 females. Mean age 23.3 yrs.	Judgmental task in which participants had to attend to the appropriateness of facial affects as opposed to gender matching tasks.	Facial affect appropriateness task produced activation in medial frontal cortex (BA8), left temporal pole, left inferior frontal gyrus and left thalamus compared to the gender matching task. Authors conclude that: The brain system involved in ToM plays a key role in judging the appropriateness of facial effect in an emotionally laden situation. Common neural substrates are involved in performing diverse kinds of ToM tasks irrespective of perceptual modalities and the emotional salience of test materials.
(49) Vollm *et al.*, (2006) fMRI	13 healthy right handed male participants.	Comic strip series (from Sarfati et al., 1997 and Brunet el al., 2000): ToM Empathy Physical causality one character Physical causality two characters.	ToM and empathy stimuli were associated with a overlapping but distinct circuits. Shared regions included mPFC, TPJ and temporal poles. Compared to empathy condition, ToM condition activated lateral orbitofrontal cortex, middle frontal gyrus, cuneus and STG. Empathy condition activated paracingulate, anterior and posterior cingulate and amygdala. Distinction between ToM circuitry and emotional circuitry.

3.5 Brain regions utilised in mentalising

The use of imaging techniques has allowed the underlying neural activations of mentalising to be observed. From these studies, several brain regions have been observed to be consistently activated in the aspects of the tasks that require mentalising, both that of self and of others. This neural network includes the frontal lobes; the temporal lobes (which have further distinct regions of the STS, TPJ and STG), the anterior cingulate cortex, the inferior parietal cortex, (for detailed reviews see (13,17,26,96,188,219-221)). These regions are activated regardless of the modality of task used (pictorial vs. verbal) and it therefore appears that Sarfati (102), when comparing the different ToM neuropsychological tasks, was correct in assuming that it is valid to compare both types of modality. These regions will be discussed in more detail in the proceeding chapter.

3.5.1 Proposed circuits for mentalising

These findings of particular brain region activations in relation to mentalising stimuli have led to proposals of specific ToM circuits.

Frith and Frith (219,220) have proposed two functionally separate neural networks. A 'dorsal' system is proposed to connect the medial PFC, the anterior cingulate and the STS. This circuit is alleged to be crucial for ToM, self-monitoring and biological motion perception. A 'ventral' system links the orbitofrontal cortex and regions next to the amygdala and is alleged to be involved in emotion and face recognition. Abu-Akel (17) proposes a distributed mentalising network split into regions that are primarily involved in the attribution of mental states to oneself, those for others and regions that are involved in both attribution aspects. These regions and the circuit

they form are allegedly organised such that: (1) representation of an individuals own mental state is subserved by the inferior parietal lobule region, (2) representation of the mental states of others' is subserved by the STS region, (3) mental states represented in these regions are then fed forward to the limbic-paralimbic system where socioemotional regulation and interpretation is conducted and finally (4) processed information is then projected to the MPFC and inferolateral frontal cortex regions for application processing.

3.5.2 Neuroimaging of ToM tasks in schizophrenia

There is currently a real paucity of investigations into mentalising dysfunction in schizophrenia. It is perhaps surprising that so few ToM schizophrenia imaging studies have been undertaken given the relatively large number of ToM neuropsychological investigations that have been published.

Prior to this thesis, the only fMRI investigation into schizophrenia and mentalising abilities was that of Russell et al., (198). This study investigated compared the performance of five right handed individuals with schizophrenia to that of seven controls on the 'Eyes' task (222). This task required participants to choose one of two words that best described the mental state of another person whose eye region was only depicted on a screen. In the control condition participants were required to judge the gender of a person from the eyes. It was found that relative to the controls, the schizophrenia group showed a significant underactivation in the left inferior frontal gyrus (BA 44/45) and left middle frontal cortex (BA9) but not in the amygdala.

In two PET studies, Brunet et al., (117,195) used a pictorial paradigm requiring the attribution of intent to characters contained within picture stories. In the former

study, five individuals with schizophrenia were compared to eight control participants and the schizophrenia group failed to activate their right prefrontal cortex relative to the control group. This failure to activate this particular brain region was observed in the latter study in which seven medicated schizophrenia patients were compared to 8 healthy controls. This second study also had two matched physical logic tasks, one with and one without human figures. Both groups showed enhanced bilateral activation of occipitotemporal and posterior portion of the STS in the task with human figures.

These studies have low numbers of individuals with schizophrenia, too low for patients to be meaningfully grouped according to symptomatology. In the fMRI study of Russell et al., (198) the ToM effects were confounded with word reading.

More imaging studies are required investigating schizophrenia and ToM such that it can be further elucidated, by comparison to the activations in healthy individuals, what the underlying functional anatomy is of compromised mentalising abilities in this form of psychosis.

3.6 Conclusions

ToM can be viewed to constitute an innate cognitive capacity represented in an innate neural network (221). The use of neuroimaging methods has shown several brain regions that consistently appear to be functionally related to mentalising abilities, and has allowed neural circuits pertaining to this aspect of social cognition to be both proposed and further investigated.

4 Pilot Study

4.1 Aim

The aim of this study was to pilot the Gallagher et al., (197) jokes that we had been kindly allowed to use by Dr Helen Gallagher. We tested these jokes on a group of individuals with schizophrenia and a matched control group in order to see if the participants, particularly the schizophrenia group, could understand the jokes. If this clinical group could get these jokes, then we believed that this would mean that members of the EHRS could and consequently these visual jokes were valid stimuli for use in an fMRI paradigm. We aimed to remove any jokes that appeared to be too difficult or ambiguous to understand by timing individuals' responses to the jokes, marking their responses and asking them to grade each joke for difficulty and humour. By timing participants' responses we aimed to derive an approximate value for the length of stimuli presentation in the proposed fMRI investigation.

Furthermore, we were in a position to compare the performance of a schizophrenia group against a control group on a ToM neuropsychological task. We would also look at effects of current symptomatology of the schizophrenia group on ToM performance, particularly the positive features of delusions and hallucinations.

4.2 Background

Prior to their imaging study on six healthy male right handed participants, Gallagher et al., (197) also conducted a pilot study of 20 normal subjects in order to investigate whether the jokes were valid stimuli in that they were funny and people could understand them. They also timed participant's responses to the jokes in order to calculate a stimulus presentation time in the fMRI paradigm.

Corcoran and Frith (100) used a visual joke paradigm to investigate the appreciation of visual jokes in individuals with schizophrenia compared to controls. There were two small sets of ToM and Physical jokes of 10 jokes per condition. Their relatively large initial schizophrenia cohort (n=44) was split into smaller groups on the basis of symptomatology by a PSE. The schizophrenia patients found the ToM jokes significantly more difficult to understand. This was more pronounced in the patients with behavioural disorders and those with passivity experiences. Those patients in remission (symptom free) showed however a normal performance and the control group had no difference in their comprehension of both joke types.

4.3 Humour appreciation

The jokes used in this pilot study conveyed both meaning and humour. Humour provides an effective means of communicating a range of ideas, feelings and opinions, and can be viewed as an integral aspect of humanity. The laughter and feeling of happiness and well being it can elicit is alleged to have health benefits. According to Foot (223) there are six basic ways in which we may use humour as a social skill: as a means of searching for information about others, as a means of giving information about oneself, in interpersonal control, in managing anxiety and in changing and sustaining social attitudes.

The study of humour appreciation in psychosis is an established region of investigation and poor performance in schizophrenics has been previously reported (e.g. (100,224)). The intentional nature of all jokes as vehicles of humour has led people to postulate that they require two stages of processing before their intention becomes clear.

According to the incongruity theory (225), humour involves the perception of incongruity or paradox in a playful context. For something to be funny, two stages are distinguished in the processing of humorous material. In the first stage, the perceiver finds his expectation about the text disconfirmed by the ending of the joke, such that the recipient encounters an incongruity, the punch line. In the second stage, the perceiver engages in a form of problem solving to find a cognitive rule which makes the punch line follow from the main part of the joke and reconciles the incongruous parts (as reviewed in (226)). In the context of pictorial jokes such as the ones utilized in this study, we must first appreciate that the joke is intended to be funny and then we must infer from the visual context of the cartoon what it is that is supposed to be funny and why it is funny. Corcoran et al., (100) define these two humour processing stages as the general intentional inference and the specific intentional inference. Crucially, the authors posit that both these stages require mentalising ability. Shammi and Stuss (227) elaborate this two stage idea and differentiate between humour comprehension and humour appreciation in an experimental setting. They describe humour comprehension as the ability to cognitively or intellectually understand humorous material. This can be assessed via the ability of a responder to select appropriate punch lines for jokes or to provide appropriate logical reasoning as to why a stimulus is humorous. It may be presumed that cognitive abilities such as language processing (for verbal humorous stimuli), perceptual processing (for visual humorous stimuli), abstract reasoning, mental flexibility, and working memory, underlie intact cognitive comprehension of humour. In contrast, 'humour appreciation' may refer to the affective response to the humorous stimuli, once the humour has been cognitively processed and understood

at some level, and may include ratings of funniness assigned to stimuli, as well as responses of mirth, such as smiling and laughing. It is therefore apparent that the perception of humour is dependent on certain faculties of the brain (e.g. attention, working memory, mental flexibility, emotional evaluation, verbal abstraction and the feeling of positive emotions). Some believe humour appreciation to be a problem solving process (228). Wild et al., (226) make an eloquent attempt to explain the various processes that occur when elements of humour are presented to an observer. Firstly, the perception of elements of humour can (or cannot, as the case may be) result in the feeling that something is funny. If the feeling that something is funny is generated, this transitory feeling can then be fed into an emotion, which in turn may influence mood. The humour response can elicit a smile or frown; it may even do the opposite. Further, the responses to humour do not have to be initiated by jokes or joke-like constructions but rather can be induced by a variety of means. These distinctions are highlighted as important by the authors, as not everything that (i) contains the potential elements of humour is (ii) perceived as humorous and leads to (iii) exhilaration, (iv) the motor expression of laughter and (v) to an elevated mood. Humour processing appears to be a complex higher mental ability and is comprised of the contribution and interaction of several processes including ToM.

4.4 Methods

4.4.1 Participants

Forty participants aged from 19-65 years were recruited for this study. Twenty of these had a diagnosis of DSM IV schizophrenia. These were either in-patients of an acute psychiatric ward, or outpatients attending clinics at the Royal Edinburgh

Hospital. They were all receiving antipsychotic medication. Twenty healthy volunteers from various community and hospital sources were also recruited as a control group. An estimate of their current level of overall intellectual function was made using the Quick Test (229). Participant demographic characteristics are shown in Table 4.1 and the clinical details of psychiatric participants can be seen in Table 4.2.

Table 4.1 Demographic characteristics-mean (SD) - of the subject groups

Group	*n* (m:f)	Age	Estimated IQ	Years of Education
Schizophrenia	20 (12:8)	39.8 (11.6)	97 (9.5)	13.3 (2.9)
Control	20 (11:9)	39.8 (13.2)	100 (7.7)	13.5 (2.5)

Table 4.2 Clinical details of the schizophrenia group

Age of onset Mean (sd)	Duration of illness(yrs) Mean (sd)	Number of admissions Mean (sd)	Medication Typical Antipsychotics	Atypical
28.4 (10.6)	10.9 (11)	8.85 (13.2)	40%	60%

To assess their present symptomatology, the schizophrenia patients were assessed on the Krawiecka Standardized Scale for Rating Chronic Psychotic Patients (230). Symptoms present over the previous week, or signs at interview, are assigned a score on a five-point scale (where 0 = absent, 1 = mild, 2 = moderate, 3 = marked, 4 = severe). Ratings are given for four positive symptoms (coherently expressed delusions, hallucinations, incoherence and irrelevance of speech and incongruity),

two negative symptoms (poverty of speech and flattened behaviour) and three non specific symptoms (depression, anxiety and psychomotor retardation). As a result, the maximum scores obtainable were 16 for positive symptoms, 8 for negative symptoms and 12 for non specific symptoms. The Krawiecka scores were also used to investigate in more detail the effect specific positive symptomatology had on ToM capabilities: the scores out of four given for delusions and hallucinations were used in this analysis.

All participants in this study gave written, informed consent.

4.4.2 The Task

There were sixty-three single-image black and white cartoon jokes, printed on A4 cards and laminated, to be piloted on the groups. Thirty-one of these were designated to be 'theory of mind cartoons'. Understanding the humour in these jokes required the attribution of ignorance, false belief or deception to one of its characters and therefore, an analysis of their mental state. The other 32 jokes were physical ("slapstick") or behavioral in nature and subsequently did not require mental state attribution for their correct interpretation. All of the images were caption-less. Examples of each type are shown below.

It was explained to the subjects that they would be shown cartoons intended to be funny. The two complete sets of cartoons were then shown to each subject in turn. The order in which they were presented was alternated so that half the participants viewed the ToM cartoons first, and half viewed the ToM cartoons second.

The subjects were shown each joke one by one and instructed to indicate to the observer when they believed they had understood its meaning. This response time

was then recorded to the nearest second using a stopwatch. The participants then gave a short explanation of their interpretation of the joke's meaning. Responses were scored 1 for a correct answer and 0 for an incorrect answer. For a theory of mind answer to be correct, appropriate mental state language had to be used. Simple physical descriptions of the scenario were required for the physical joke responses to be scored correct. Examples of appropriate and inappropriate responses for two of the cartoon stimuli, representing one example from the two cartoon conditions, are shown in Figure 4.1.

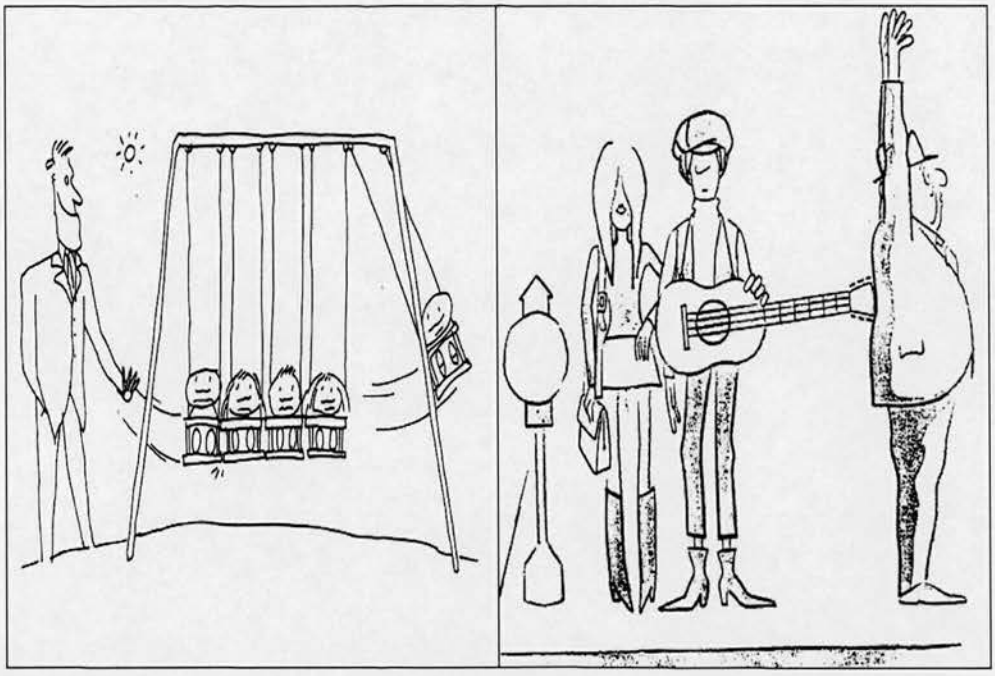


Figure 4.1 An example from the physical jokes subset. (b) An example from the ToM jokes subset.

Physical joke: Examples of acceptable responses

'The man is using the swing like a giant Newton's cradle'

'The children are swinging against each other, like one of those desk toys'

Examples of unacceptable responses

'The man is happy because the children are on the swings'

'The man wants to send him on the end flying off the swing, so that he gets hurt'

Theory of Mind joke: Examples of acceptable responses

'The man thinks that someone is putting a gun in his back, but it's a guitar'

'The couple doesn't realize that they are making the man think he is being robbed'

Unacceptable responses (i.e. no mental-state attributions made)

'The couple are waiting for a bus and the man is jumping to reach something'

'The couple are trying to push the man over with the guitar so they can get on the bus first'

Furthermore, participants were asked to subjectively grade each cartoon image for humour and difficulty on a scale of 1-5, where 1 was not funny or very easy and 5 very funny or very difficult respectively.

Tests were all performed in quiet, distraction-free rooms.

4.5 Statistical analysis

Data analysis was performed using SPSS for Windows Version 11.0.

General linear model repeated measures ANOVA was used to determine the significance of any difference in the Physical versus ToM scores seen between the groups. General linear model ANCOVA controlling for Physical joke score was used to investigate the selectivity of any group differences in ToM capabilities. Linear regression analysis was used to relate physical and ToM scores to Krawiecka sub-totals for positive, negative and non specific symptoms, individual Krawiecka symptoms, medication dose and joke block presentation order. Independent two-tailed t-tests were used to compare the group score differences in the two conditions (when carrying out simple contrasts following the general linear model repeated measures ANOVA), the average subjective ratings for humour and difficulty assigned to the stimuli by the participants, and the average response times to get the jokes.

4.6 Results

4.6.1 Patients with schizophrenia compared to controls

Using general linear model, repeated measures ANOVA, highly significant main effects were found for repeated measure (i.e. joke type: $F=112.9$, $P<0.0001$) and group effect ($F=42.6$, $P<0.0001$) as well as a significant interaction of group by joke ($F=10.3$, $P=0.003$). This is summarized in Table 4.3.

Follow-up t-tests comparing individuals with schizophrenia to controls were highly significant for both the ToM condition ($P<0.0001$) and the physical condition ($P<0.001$).

Additionally, within both the patient and control groups, scores were significantly worse for ToM jokes than physical jokes ($P< 0.0001$ for both groups). However, the significant interaction showed that the difference of 10.6 for the patient group was greater than that for the controls (5.6). Using the general linear model, ANCOVA, controlling for Physical joke score, a significant group difference on ToM joke scores was still evident, $F=19.5$, $P<0.05$.

The two groups were well matched for age, IQ and sex, and any difference between them was shown to be insignificant by independent 2-tailed t-test ($P > 0.1$). It was unnecessary, therefore, to perform regression analyses to co-vary for these factors.

Table 4.3 Performance on Physical and ToM jokes between the study groups

	Physical jokes score mean (sd)	ToM jokes score mean (sd)
Schizophrenia Group	23.3 (4.5)	12.7 (6.2)
Controls	28.2 (2.94)	22.6 (2.4)

4.6.2 Subjective Joke ratings and Response times and order of joke set presentation

It was found via independent t-test analysis that there was no significant difference between the schizophrenia patients and control participants' subjective ratings for humour and difficulty or between the average response times of correct responses ($P > 0.05$).

Furthermore, linear regression indicated that the order of presentation of the joke sets had no significant effect on ToM or Physical joke scores. Results are summarized in Table 4.4.

Table 4.4 Subjectivity scores and response times

	Picture Condition	Average humour score	Average difficulty score	Average time for correct responses
Controls	Physical	2.3 (.48)	1.9 (.62)	5.04 (2.2)
	ToM	2.4 (.35)	1.9 (.57)	5.2 (2.9)
Schizophrenia Group	Physical	2.4 (.47)	2.4 (.68)	7.2 (2.5)
	ToM	2.6 (.42)	2.4 (.66)	6.8 (2.7)

NB: Values are means; standard deviations in parentheses.

4.6.3 Symptoms

Correlations were run to investigate the relationships between performances on ToM and physical jokes and different symptom scores (assessed on the Krawiecka five-point scale). These data are displayed in Table 4.5.

As stated, performance was not significantly reduced in association with increasing severity of positive or negative symptoms as a whole or delusions and hallucinations specifically. The features of depression, incoherence and poverty of speech were also analysed to see if they could be having an effect on the patients ToM and physical joke performance but were found to be non significant on both conditions.

Table 4.5 Krawiecka symptom scores in patients with schizophrenia and their association with performance on ToM and Physical joke conditions.

	N	Mean Krawiecka Score	SD	ToM Sig. (regression)	Physical Sig. (regression)
Positive symptoms	20	5.0	3.2	0.903	0.879
Negative Symptoms	20	1.6	1.8	0.651	0.951
Non specific Symptoms	20	1.6	1.8	0.676	0.509
Delusions	20	2.5	1.6	0.520	0.728
Hallucination	20	1.9	1.7	0.825	0.466
Depression	20	0.65	0.875	0.191	0.347
Incoherence of Speech	20	0.3	0.657	0.413	0.684
Poverty of Speech	20	0.45	0.826	0.433	0.669

*None of these correlations reach significance

4.6.4 Medication

Antipsychotic medication dose at time of testing was recorded for each patient and using standard published tables (231,232) was converted into daily chlorpromazine equivalent dosage. This measure was correlated to performance and was found to be non significant in both cartoon conditions.

4.7 Discussion

This study was designed to pilot images that were intended to be used as stimuli in a visual joke fMRI study that would investigate neural activations between a representative sample of the EHRS cohort and matched controls. Although Gallagher et al., (197) piloted these cartoons behaviourally in a similar manner, they only tested and consequently imaged a group of healthy control participants. We believed that a further pilot study of these same images was required in order to assess the ability of a psychotic clinical group on this task. We were primarily interested to see whether schizophrenic participants could manage the task, as it had to be ascertained whether these stimuli were viable for use in the later planned fMRI experiment. We intended to compare EHRS participants who had experienced transient and isolated psychotic symptoms, those who had not experienced such symptoms, a matched control group and a subgroup of EHRS who had started the study as well but had then gone on to develop a DSM-IV diagnosis of schizophrenia. We reasoned that if the schizophrenia group in this pilot study could deal with the task demands, then the EHRS participants would also be able to.

4.7.1 Joke scores, grading and reaction times.

The schizophrenia group, although performing significantly differently from the control group, generally appeared to be able to successfully undertake the task, in that they understood the majority of the jokes and could assign subjective gradings to them. The reasons for these significant group differences and possible interpretations as to why they were present are discussed in detail below.

Using individual scores for each group, we could clearly see what jokes participants were consistently failing on, regardless of what group they belonged to. These jokes were seemingly incomprehensible such that the majority of participants could not give an attempted interpretation of the joke and would pass on them. These jokes were also given high grades for difficulty level and low grades for humour level. By using participant scores and subjective gradings, we removed the most difficult 7 ToM cartoons and 8 Physical cartoons from the original experimental pool leaving us with two sets of 24 cartoons for each type. These would then be used as stimuli in the later fMRI study.

The reaction time data showed that controls were approximately 2 seconds faster with their responses than the schizophrenia group for each of the two cartoon types, although this difference was not significant. These timing means and accompanying standard deviations would be used to calculate how long each visual joke image would be displayed to participants for in the fMRI paradigm.

4.7.2 Schizophrenia subjects compared to controls

This study showed that individuals with schizophrenia and normal IQ had a poorer understanding of both types of jokes (and at least a reduced ability to relay their humorous intent) than matched healthy controls. This is to be expected, as

schizophrenia patients have previously been reported to show poor appreciation of humour (described in (100)). It seems unlikely that this is explained by depression or indeed any other symptoms, as regression analysis showed it not to be significantly related to poor ToM performance.

However, the difference between the physical and ToM joke scores was significantly greater for schizophrenia patients, than controls. This implies that it is some aspect of the disease process that is associated with ToM capability, rather than simply a task difficulty effect.

If the schizophrenia group had a poorer understanding of the jokes then we would expect this to be reflected in the subjective gradings for humour and difficulty. As shown in Table 4.4, the schizophrenia group actually graded the jokes slightly higher for both humour and difficulty. Furthermore, despite both groups performing significantly worse in the ToM condition than in the physical condition, they both graded the two joke sets as equally difficult. Possible explanations for this could be that people were instructed that the cartoons were meant to be funny and so consequently may have stated that a joke was humorous even if they didn't find a joke funny.

The subjective gradings of the jokes did not necessarily require a correct understanding of the joke for a numerical value for humour and difficulty to be assigned. Everyone could give numerical gradings for a joke but not everyone could correctly describe the jokes or use the relevant mentalising language in their joke description.

It was found that both groups found the ToM jokes significantly more difficult than the physical ones. The former were certainly more detailed and by their very nature

were comprised of characters in ToM scenarios. It could be that these jokes were more difficult to understand, but there was no significant difference between the response times of the two joke types for either group. Poor verbal report of mentalistic terms may be an intrinsic feature of schizophrenia and this could have resulted in this study's schizophrenia group's poor performance on this set of jokes. Language and thought are intrinsically linked and the question arises as to whether disordered verbalisation in schizophrenia is a speech disturbance only or part of a disorder in thinking (as discussed in (233)). Likewise, the observed ToM deficit seen in this study could reflect a lack of response in mentalistic terms, related either to a specific deficit in inferential skills or to a more general inability to verbalise other's mental states. Verbalization abilities may be dramatically impoverished in schizophrenia and may constitute an experimental limitation or bias, especially in those individuals with negative features and thought and language disorders (234). Poor verbal report, especially when the production of mentalistic terms is expected, is an extrinsic feature of schizophrenia. Verbalizable knowledge refers to task-related information that is potentially conscious and expressable in language, and a basic problem is that it is difficult to prove that a lack of response in mentalistic terms is related either to a specific deficit of inferential skills to a more general inability to verbalize other's mental states. It appears that the core nature of the relationship between language and the attribution of mental states is still unknown (103).

As regards our patients' verbalisation skills, they all scored none or low Krawiecka scores for the symptoms of poverty of speech and incoherence/irrelevance of speech.

We therefore believe that their poor performance was the result of a compromised ToM function rather than a verbalization expression deficit.

This data suggests that, as predicted, schizophrenia patients have problems in interpreting the thoughts of others, supporting the findings of previous work (e.g. (100)). The closely matched demographic characteristics of the two groups, suggests that problems in 'mentalising' evident in schizophrenia, are not simply attributable to the influence of factors such as age, sex and, importantly, IQ.

There is, however, an alternative interpretation to these results in that the individuals with schizophrenia may not be showing a domain – specific difficulty with ToM function but rather may be performing differentially more poorly than the control group on the more difficult ToM condition, such that the observed deficit could reflect a differential sensitivity to task difficulty.

4.7.3 Symptom specific findings

When the obtained totals for positive Krawiecka symptoms were analysed it was found that there was not a significant relationship between higher positive symptomatology and poor ToM performance, contrary to what had been predicted. Closer scrutiny of individual positive symptoms also revealed that neither delusions and hallucinations nor speech incoherence was significantly linked to an impaired ToM performance. Previous studies have shown paranoid delusions to be significantly related to poor ToM performance, in both first and second order ToM tasks and in both verbal and pictorial paradigms (98-100). Interestingly, Langdon et al., (115) also using a pictorial paradigm, found no evidence linking poor mentalising capabilities to positive symptoms.

These findings might be attributed to several individuals who despite scoring the maximum Krawiecka score (4) for delusions, hallucinations or both, performed similarly to controls in the ToM condition. Alternatively, our patients' delusions and hallucinations may not be those specifically implicated in ToM impairment.

Unlike the findings of previous research, negative features of schizophrenia were not associated with ToM capabilities. However, the mean Krawiecka scores for these features were low within the subject group, and our number of subjects was relatively small. Such ratings can however be both unreliable and too noisy to show a relationship that a more sensitive test, such as fMRI, might show.

4.7.4 Limitations and further work

This study was highly effective as a pilot study investigating whether prospective stimuli for a proposed fMRI investigation were indeed acceptable stimuli. However, as a neuropsychological investigation into ToM capabilities within a schizophrenia group compared to a control group, it did have limitations.

With its relatively small sample size, this study was limited, especially for symptom sub-groups analyses, although we did find disease effects. With a larger sample, further symptom-specific sub-groups could be made (e.g. different types of delusions or hallucinations, formal thought disorder, different aspects of negative symptomatology, etc). Furthermore, another control group of non-schizophrenia, psychiatric patients may have been useful to explore more closely the role of diagnosis as opposed to symptoms. One of our previous studies (133) used a psychiatric control group of patients with a psychotic affective disorder and found that positive psychotic symptomatology was linked to poor ToM performance and

was not diagnosis specific. This implies that ToM deficits are not necessarily specific to schizophrenia but could be related to psychoses and specifically to the positive symptoms of delusions and hallucinations.

Although we did not compare task performance by including a non-mentalising task, such as an executive function task, we believe that the physical cartoons themselves acted as an adequate internal control. If the schizophrenia group had performed as poorly on the Physical cartoons as the ToM cartoon condition, then this could imply either a verbalisation deficit or general cognitive impairment. However, as mentioned previously, regression analysis showed no significance for language impairment using the Krawiecka symptoms of poverty of speech and incoherence of speech and poor ToM jokes performance. ANCOVA showed that the group differences on the physical ToM jokes could not be accounted for by the group differences on the physical jokes. This was taken as evidence of an observable compromised ToM capacity within the schizophrenia group.

An unrelated cognitive neuropsychological task could have been implemented testing another cognitive domain (e.g. executive function, working memory) and this could have been used to further elaborate whether the observed alleged compromised ToM function was a specific deficit or secondary to general cognitive impairment (see for example, (113,115), who used the Tower of London task in this way). However, there was no significant group difference for IQ in this particular study.

4.8 Conclusions

Further research is then required in ToM and schizophrenia to see whether the presence of schizophrenia itself is enough to impair mentalising capabilities or whether the impairment is due to specific symptoms. The deficits observed in

schizophrenia, could be state (related to fluctuating symptom severity) or trait in nature.

This pilot study enabled us to realize that the visual joke stimuli were valid for use with a clinical population and we were able to remove the jokes that had proved to be too difficult for participants to comprehend. We were able to compare and contrast in detail the performance of this schizophrenia group with a matched control group. The schizophrenia group performed significantly worse in both the physical and ToM conditions on this visual joke task than the controls. The performance on the ToM condition was significantly worse and is taken as evidence for a compromised ToM capability in the schizophrenia group which is in keeping with previous research. In this instance poor ToM performance could not be significantly linked to any particular symptomatology as had been hypothesised.

5 fMRI ToM investigation

5.1 Aims

The aim of this particular study was to investigate the neural correlates of high risk individuals compared to controls on an fMRI visual joke task. As far as we are aware this is the first time such a task had been employed on such a clinical population. Similar to the previous neuropsychological investigation, by splitting the HR group on the basis of symptomatology, we aimed to investigate whether differences in activations could be due to state or trait effects.

5.2 Background

Imaging studies of schizophrenia have found both structural and functional abnormalities, some of which are evident to some extent in unaffected relatives (139,140,144,235,236). Cognitive deficits have been observed in relatives of affected individuals when compared to healthy controls on neuropsychological tests (150,169,237). The few studies using neuropsychological mentalising tasks in relatives have found evidence both for reduced mentalising capabilities in unaffected relatives (119) and no evidence for such a phenomenon (148). We found evidence for both a state and trait effect in these very participants on a small battery of ToM and self-monitoring tasks previously discussed (238).

In the few previous high risk relative imaging studies, prefrontal cortex activation differences in the high risk relative groups have been observed. In a small study, Keshavan et al., (239) compared activation patterns in four high risk subjects and four controls performing a memory guided saccade task. Hypofunction of bilateral dorsolateral prefrontal cortex, right middle frontal gyrus and right inferior parietal cortex was observed in the high risk relatives compared to the controls. In a larger

study, in which 23 high risk subjects and 18 healthy controls performed the *n*-back working memory task, the unaffected relatives were observed to exhibit an increased response in the right dorsolateral prefrontal cortex. This was then replicated by the authors in a second analysis of 25 high risk relatives and 15 controls (240). Thermenos et al., (241) compared 12 high risk relatives and 12 controls on their performance on an auditory working memory task. The relatives showed increased activation of the prefrontal cortex and thalamus. However, after controlling for task performance, greater activation was of the anterior cingulate region was reported in the relatives.

A SPECT study comparing schizophrenia patients, their asymptomatic 'high risk' relatives and a control group, on memory function found that the schizophrenia and relative group exhibited reduced perfusion in left inferior prefrontal and anterior cingulate cortex (242).

Structural differences have also been observed in relative groups. For example, O'Driscoll et al., (243) compared healthy relatives of schizophrenic patients to matched healthy controls on verbal memory and amydala-hippocampal (AHC) volume. It was found that the relatives had significantly poorer delayed verbal memory and reduced AHC volume than the controls. This region was also found to be smaller compared to controls but increased in comparison to patient groups in the EHRS cohort (143,144).

Gallagher et al., (197) used a combined visual joke and verbal short story ToM imaging paradigm on a group of 6 healthy controls to investigate brain regions activated by the two different ToM modalities. In the visual joke condition, significant activations were observed in the medial prefrontal and right middle

frontal and fusiform gyri, right temporo parietal junction, and the precuneus, compared to those visual jokes that did not require mentalising abilities.

Using the same visual joke paradigm as Gallagher et al., (197) we hypothesized that significant group differences would be found in the Superior Temporal Sulcus (STS), temporal poles and prefrontal cortex (both medial and dorsolateral) with the High Risk relatives, particularly those who had and those who were experiencing psychotic symptoms, exhibiting different activation patterns compared to the controls. These three areas have previously been identified as key regions involved in a mentalising 'circuit' (e.g. (26,221).

As far as we are aware, this is the first time relatives of individuals with schizophrenia have been investigated using a theory of mind fMRI paradigm.

5.3 Methods

5.3.1 Study population

Initially, forty three age and IQ matched individuals belonging to the Edinburgh High Risk Study (78,136) were recruited and imaged. These were the same participants who undertook the previously discussed self-monitoring and ToM tasks. Unfortunately, one individual's scan was unable to be reconstructed and consequently could not be used in the subsequent analyses. This resulted in the HR- group being reduced from 13 to 12 participants. Apart from this change, the groups were the same and split due to presence and absence of symptoms at the PSE (137) as previously described such that:

HR+ (n=12): individuals who had reported transient psychotic symptoms in at least one PSE interview during their participation in the EHRS.

HR- (n=12): individuals who had never reported any transient psychotic symptoms during PSE interview.

For a secondary analysis investigating symptomatology, the HR+ group was then further split into the following two groups based on past or present psychotic symptoms:

HR+Now (n=6): individuals who reported transient psychotic symptoms, usually isolated delusions or hallucinations, on the day of testing.

HR+Ever (n=6): individuals had reported transient psychotic symptoms in a previous PSE interview but not in the one on the day of imaging.

In addition, a group of five individuals who had initially been high risk but had developed schizophrenia were recruited.

HRIll (n=5): individuals who had started their participation in the Edinburgh High Risk Study as well and had then gone on to develop a DSM IV (1994) diagnosis of schizophrenia. Of these, 3 were on medication at the time of testing, whilst one had never taken antipsychotic medication and the other had during a brief hospital admission 3 years previously and had been medication free since.

All participants provided written informed consent, and the study was approved by the Psychiatry and Clinical Psychology subcommittee of the Lothian research ethics committee.

The participant demographic details can be viewed in Table 5.1.

5.3.2 Scanning procedure

Imaging was carried out at the Brain Imaging Research Centre for Scotland (Edinburgh, UK) on a GE 1.5 T Signa scanner (GE Medical, Milwaukee, WI, USA) equipped with 22 mT/m 'Echospeed' gradients having a rise time of 200 μs. The subjects wore ear defenders and were given an emergency buzzer. After a localizer scan, subjects were imaged with an axial T2-weighted fast spin-echo sequence [repetition time/echo time (TR/TE) = 6300/102 ms]. Twenty slices (5-mm thickness, 1.5-mm gap), aligned parallel to the anterior commisure-posterior commisure (AC-PC) line, covered the brain. A structural scan in the coronal plane aligned perpendicular to the AC-PC line with 1-mm pixel size was then acquired using a 3D inversion recovery-prepared T1-weighted fast gradient echo volume sequence [inversion time (TI) = 600 ms; Flip angle 15 degrees TE Minimum]. One hundred and twenty-four slices (thickness 1.7 mm) were aligned perpendicular to the AC-PC line.

Finally, axial gradient-echo echo planar images (EPI) [TR/TE = 2500/40 ms; matrix 64 x 64; field of view (FOV) 220 x 220 mm] were acquired continually during the experimental paradigm. Twenty-eight contiguous 5 mm slices were acquired within each TR period. Each EPI acquisition was run for 292 volumes, of which the first four volumes were discarded. Visual stimuli were presented using a screen (IFIS-SA, Invivo, Orlando, FL, USA) placed in the bore of the magnet; corrective lenses were used when necessary. Subjects were provided with left- or right hand pushbutton units (IFIS-SA, Invivo, Orlando, FL, USA) depending on their preference, to allow their reaction times to be logged by the software.

5.3.3 Experimental Task

The task consisted of a blocked paradigm comprising 3 conditions of black and white caption-less cartoon images. Our task was based on that of Gallagher et al., (197) and the same cartoon stimuli were used, generously donated by the authors of that study. We had piloted the cartoon images on a group of healthy controls and a schizophrenia group and removed those images that were deemed to difficult or ambiguous to understand the joke contained within (see pilot study chapter and (125)). The conditions were as follows:

ToM joke condition in which understanding the humour contained within the images required the attribution of false belief, ignorance or deception.

Physical joke condition containing images of slapstick humour which did not require ToM abilities to understand the jokes.

Jumbled image condition (control condition) which was comprised of images containing randomly positioned objects, animals and people. There was no underlying narrative to these images and consequently no joke contained within them.

Examples of these 3 image types can be viewed in figure Figure 5.1.

There were 6 blocks in each condition and 4 pictures in each block. Each image was shown for 9.75 seconds. A corresponding picture prompt for the next block was shown for 1 second at the end of the fourth image of the current block, signifying what type of condition the next epoch was going to be. A picture of a brain indicated the next block would be comprised of ToM images. The same brain image with a cross through it indicated that the next block would be Physical joke images. A female face fragmented into 3 portions indicated a block of jumbled images. These

prompt images were also black and white and caption-less. These can be viewed in the Appendix.

There were 4 run types of the 18 block conditions, with the conditions presented in different orders within these runs, and these were presented in a counterbalanced order.

In the joke conditions, participants were asked to press a button when they thought they had got the joke. In the control condition, they were requested to press a button when they had seen all the components comprising the jumbled image.

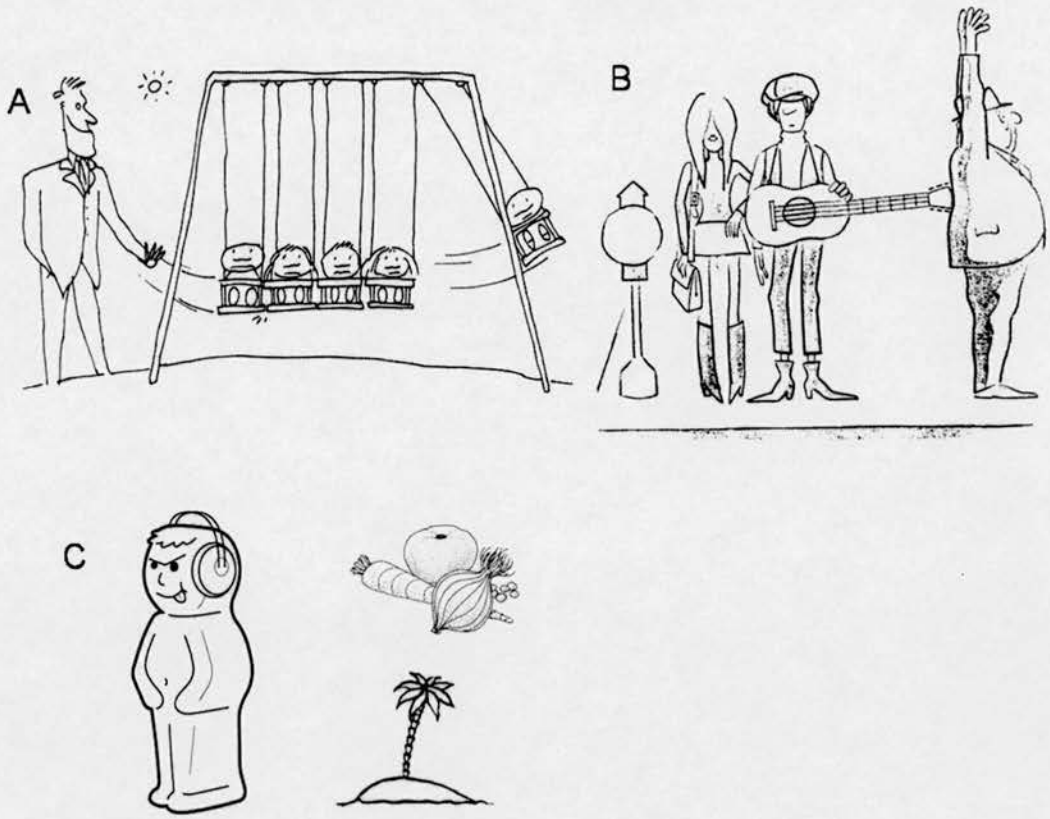
5.3.4 Behavioural data

Immediately after the scan, the participants under went a debrief in which they were shown the two sets of visual jokes in their entirety. They were asked to explain each joke and to say whether they found it easy or difficult to understand.

Correct descriptions were ticked correct whilst incorrect descriptions or passed jokes (participants seemingly having no idea about the punch line and consequently not 'getting' the joke) were marked as a cross. The joke scores were later tallied with correct responses gaining a score of 1 and incorrect responses a score of 0.

Participant reaction times (RT's) for pressing a button to signify when they thought that they had got the jokes were obtained from the participant's relevant scan IFIS file.

Figure 5.1 (A) An example from the Physical jokes subset. (B) An example from the ToM jokes subset. (C) An example from the jumbled (control) image subset. All the stimuli images can be viewed in the Appendix.



5.3.5 Scan processing

The EPI images were reconstructed offline into ANALYZE format (Mayo foundation, Rochester, MN, USA). Scan analysis was performed using SPM2 (The Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London, http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab, version 6.5.1 (The Mathworks, Natick, MA, USA).

5.3.6 Pre-processing

In order to be sure that the brain magnetisation had reached a steady state prior to the onset of the paradigm, the first four initial volumes were discarded. Consequently,

there was a 10 s delay before the initial onset of the stimuli to allow for these discarded acquisitions.

For each participant, the EPI volumes were realigned to the mean volume of the series. The first step of the realignment process involved estimating the 6 parameters of the rigid body affine transformations that minimise the sum of the squared differences between each scan and the reference image, and then applying these transformations to the images. The purpose of this step is to attempt to correct for movement throughout the period of image acquisition or 'run'. Information in graphical and text format regarding the extent of subject movement that is corrected (translation and rotation in x, y and z) is provided. The graphical output in SPM for each subject from this stage of pre-processing was visually inspected for drifts, periodic events, and spikes. Further analysis of participant movement data was investigated by employing two matlab scripts, 'rd_motion.m' (written by Dr K Christoff available online http://www-psy.stanford.edu/~kalina/), and 'cc.m' (written by Dr E Siminotto,). These summarised the absolute maximum extent of movement and identified if there was significant correlation between movement parameters and task regressors, respectively.

Head motion is a potential and serious confound of fMRI studies. It has been reported that schizophrenia groups are liable to move more than the control groups in imaging studies (244), though this is usually in the x plane rather then the z plane. There was no reason to exclude anyone on the basis of head movement or movement correlated to presentation of experimental stimuli.

5.3.7 Normalisation and spatial smoothing

The mean image created during the realignment stage was then used in the normalisation stage of pre-processing. The process of normalisation of images from individual subjects into a standardised space is necessary for performing group comparisons and permits the use of standard brain atlases for the reporting of results. The mean image was selected as the 'image to determine parameters', and then all images in the run were selected as the 'images to write normalised'. The images were normalized to the EHRS EPI template (created from an average of 121 EHRS participants mean fMRI images) using linear affine transformations followed by non-linear deformations, and resampled using sinc interpolation to cubic voxels of size 8 mm^3.

The use of a study specific template conveys particular advantages over the generic EPI template supplied with SPM. The two main reasons for study specific template use are that scans are normalised to a template generated from the same scanner with the same imaging parameters (e.g. intensity profiles and non-uniformities) and the template is generated from the same demographic population to that used in the study (as discussed in (140)).

The normalized images were then spatially smoothed with a 6x6x6 mm^3 full width half maximum (FWHM) Gaussian filter. This was done both to minimize residual inter-subject differences and to meet assumptions for parametric statistical analysis regarding the distribution of residuals.

Image visual inspection:

The visual inspection of images prior to the realignment stage and after pre-processing occurred to verify image quality and to ensure that the image processing

had been successfully completed. No subjects' images appeared to contain detrimental image artefact neither were there any subjects with any structural brain abnormalities (e.g. vascular malformations).

5.3.8 Statistical Analysis

5.3.8.1 First Level analysis

SPM2 implements the general linear model in the analysis of statistics. This model can be simplified as: $Y=\beta X + \epsilon$

Where Y is the observed response, i.e. the fMRI time series data; X is the linear combination of explanatory variables (also called 'covariates' or 'regressors') comprising the design matrix; β are the regression weights or parameters to be estimated for each of the explanatory variables in the design matrix; and ϵ is the residual error term.

Each column in SPM in the design matrix corresponds to effects built into the model. In this current analysis, the data was modelled with 3 conditions at the individual subject level, the two visual joke conditions and the jumbled image/control condition. Each of these conditions were modelled by a boxcar convolved with the synthetic haemodynamic response function (hrf) provided in SPM2. It is necessary to perform this convolution as if the boxcar function was not convolved it would remain a sharp transition between conditions. With convolution applied, the data is smoothed and delayed as seen in the true hrf. The resulting conditions are represented by the first 3 columns in the design matrix. The estimates of the subject's

movement from the realignment stage of pre-processing (translations and rotations in x,y, and z) were entered as 'covariates of no interest' in the model, represented by columns 4-9 in the design matrix. Before fitting the model, the subject's data was filtered in the time domain using both an AR(1) model low pass filter and a high pass filter (400 s cutoff).

The use of high and low pass filtering in the analysis of fMRI time series is used to remove low frequency drifts (such as physiological noise) and to address issues relating to serial autocorrelations seen in fMRI data. The implementation of the process of temporal smoothing is a standard technique used to correct for correlated residuals in fMRI analysis. After temporal smoothing the autocorrelation is dominated by the smoothing filter applied and can be estimated from the filter parameters.

The following contrasts were then constructed:

Those that examined the two visual joke conditions versus each other:

[1 -1 0] hereafter referred to as ToM vs. Phy

[1- 1 0] hereafter referred to as Phy vs. ToM.

Those that examined each visual joke condition versus the rest condition:

[1 0 -1] hereafter referred to as ToM vs. Con.

[-1 0 1] hereafter referred to as Con vs. ToM.

[0 1 -1] hereafter referred to as Phy vs. Con.

[0 -1 1] hereafter referred to as Con vs. Phy.

The three main contrasts of interest were:

ToM vs. Phy: this would show the significant activations for the ToM cartoons once those for the Physical cartoons had been subtracted out.

ToM vs. Con: this would show the significant activations for the ToM cartoons once those for the Jumbled images had been subtracted out.

Phy vs. Con: this would show the significant activations for the Physical cartoons once those for the Jumbled images had been subtracted out.

5.3.9 Batch scripting

In this study, the image reconstruction, pre-processing, and the first-level statistical analysis was performed using batch scripts originally devised for SPM99 use by Dr E Simontto (140) and later modified for SPM2 use by Dr D Job, based on examples provided with SPM. In general, the default settings in SPM2 were selected for the first level analysis. The two exceptions were the specification of a new study specific mask, and the inclusion of previously discussed realignment parameters.

This use of batch scripting in studies with relatively large numbers allows for the automation of aspects of scan processing and analysis and has time saving advantages.

These batch processing scripts were also edited to use a new mask image which was produced for use in previous EHRS analyses (140).

5.3.10 Second Level Analyses

Contrast images for each subject representing a subject-specific summary of brain responses to the different conditions (cartoon conditions versus each other and versus control condition) were entered into a second level random effects analysis to make inferences about activations both within and between groups. A one sample t test was

used to determine areas of activation within each of the groups and ANOVA and ANCOVA analyses were used to examine differences between groups.

For the activation clusters pertaining to this analysis, statistical maps were thresholded at a level of P=0.005 uncorrected voxel level and regions were considered significant at P<0.05 cluster level corrected for multiple comparisons.

Two participants, one from the HR- group and a control, did not engage in any button pressing during the jumbled image (control) condition. Consequently, we decided to remove these individuals from the ToM vs. Control and Phy vs. Control contrast analyses (and the corresponding inverse contrasts).

Potential confounds (sex, age and handedness) were entered as covariates in the second-level random effects analysis (ANCOVA). In the second analysis, button press reaction time (RT) was also added as a potential confound (as it was found the HR+Ever group was significantly quicker at button pressing in both the cartoon stimuli conditions.

A conjunction analysis was conducted using a script written by Dr Tom Nichols (http://www.sph.umich.edu/~nichols/Conj/, Nichols et al., 2005) in order to investigate whether observed PFC activations were in the same voxel clusters in the groups.

ToM and Physical debrief cartoon scores for both analyses were entered as covariates of interest in ANCOVA analyses to investigate whether debrief scores were significantly related to brain activations.

For all analyses, statistical maps were thresholded at a level of P=0.005 uncorrected voxel level and regions were considered significant at P<0.05 cluster level corrected for multiple comparisons. All the results reported from the analyses in this chapter

are from random effects analyses, and P values quoted in the text are at the corrected cluster level. Voxel co-ordinates were converted from MNI (Montreal Neurological Institute) to Talairich co-ordinates using a non-linear transformation script, as described in (http://www.mrc-cbu.cam.ac.uk/Imaging). Identification of brain regions was performed using the Talairach and Tournoux (245) brain atlas and the electronic resource Talairach Deamon (http://ric.uthscsa.edu/projects/talairachdaemon.html).

5.4 Results

5.4.1 Demographics

Table 5.1 shows the participant demographics. There were no significant group differences on age and IQ (P=0.075; P=0.104 respectively) and the groups were not balanced for sex or handedness. As stated previously, sex and handedness as well as age were entered in as covariates.

Table 5.1 Participant demographics

Group	*n (m:f)*	*Hand (L:R)*	*Age*	*NART IQ*
Analysis 1				
HR-	12 (8:4)	1:11	30.8 (2.1)	101.5 (8.9)
HR+	12 (5:7)	3:9	28.9 (3.7)	101.1 (9.3)
Control	13 (8:5)	0:13	29.6 (1.6)	106.8 (7.8)
Analysis 2				
HR+Ever	6 (1:5)	2:4	29.2 (3.8)	107 (5.83)
HR+Now	6 (4:2)	1:5	28.7 (8.4)	95.2 (8.42)
HRill	5 (1:5)	0:5	26.8 (4.3)	102.2 (13.4)

NB: Values are given as means: standard deviation in parentheses.

Table 5.2 shows the group reaction times and debrief scores. In analysis 1 there was no significant group difference in response times of button pressing. In analysis 2

however, the HR+Ever group was significantly quicker at button pressing than the HR+Now for the control images (P=0.034) and quicker than both the HR+Now and HRill for the ToM cartoons (P=0.006 and 0.007 respectively).

Table 5.2 Group reaction times and debrief scores

	HR-	*HR+*	*Controls*	*HR+Now*	*HR+Ever*	*HRill*
ToM RT (s)	3.54	3.46	3.66	4.35	2.56	4.38
	(0.8)	(1.1)	(1.5)	(0.6)	(0.6)	(1.1)
Phy RT (s)	3.09	3.36	3.25	4.06	2.66	3.57
	(0.7)	(1.2)	(0.7)	(1.1)	(0.8)	(0.9)
Jumbled RT (s)	3.46	3.22	2.59	4.18	2.25	3.65
	(1.5)	(1.5)	(1.1)	(1.4)	(0.9)	(1.0)
ToM debrief score 1	18.5	18.6	18.9	19.7	17.5	15.6
	(4.7)	(4.9)	(2.3)	(2.7)	(6.6)	(2.9)
ToM debrief score 2	5.0	4.6	4.8	5.3	4.7	2.6
	(1.5)	(2.3)	(2.1)	(0.5)	(2.2)	(0.5)
Phy debrief score	18.2	18.3	18.6	17.7	18.8	15.8
	(3.7)	(3.9)	(3.6)	(3.8)	(4.2)	(4.1)

NB: Values are given as means: standard deviation in parentheses.

There was no significant group difference in either analysis for Physical cartoon debrief scores. ToM debrief score 1 (ToM 1) was defined as the ability to correctly define the ToM cartoons whereas ToM debrief score 2 (ToM 2) was the ability to not only correctly define the joke but to use the relevant mentalising language. There was no significant group differences for ToM debrief score 1 in either analysis. In analysis 2, the HRill were found to score significantly less than the HR+Now on ToM debrief score 2 (P=0.017). The ToM score debrief score 2 was significantly less than the ToM debrief score 1 for all groups in both analyses (P<0.0001). When the debrief cartoon scores were entered as covariates of interest, there was no significant brain activations related to cartoon debrief scores (P>0.05).

5.4.2 Head movement

Table 5.3 details the mean head movement parameters for the groups. The HRill were found to have a significant difference in their maximum z plane movement when compared to the other groups (P=0.003). There was no significant single subject or group correlation between movement parameters and task regressors. Although an attempt was made to control for movement realignment stage of the pre-processing of the data, we cannot be absolutely certain that all movement within this group in this plane has been controlled for and this should be borne in mind when interpreting the results for this particular group. To investigate this issue further, the Z plane was entered as a covariate in the ToM vs Phy contrast of analysis 2. The significant BA8 activations of the HR+Ever activating greater than both the HR+Now and HRill groups remained. The frontal lobe activation of the HR+Now activating greater in BA9/46 than the HR+Ever, and the greater fusiform activation observed in the HR+Ever relative to the HR+Now, became non significant at the threshold of P=0.005. However, these clusters were evident at the lower threshold of P=0.05. When the Z plane movement values were added as a covariate of interest, there was no significant correlation between movement and correlation. As a result of this finding, it was decided to not have Z plane movement as a covariate in subsequent analyses.

Table 5.3 The estimate of movement parameters determined from realignment stage of pre-processing.

	HR- (n=12)	*HR+ (n=12)*	*Controls (n=13)*	*HR+Now (n=6)*	*HR+Ever (n=6)*	*HRill (n=5)*
Max movement in x (mm), (std dev)	0.19 (0.13)	0.19 (0.09)	0.19 (0.15)	0.17 (0.11)	0.19 (0.09)	0.26 (0.08)
Max movement in y (mm), (std dev)	0.97 (0.35)	0.77 (0.32)	0.65 (0.24)	0.74 (0.42)	0.79 (0.21)	0.79 (0.26)
Max movement in z (mm), (std dev)	0.98 (0.69)	0.86 (0.53)	0.76 (0.29)	1.01 (0.67)	0.72 (0.33)	1.83 (0.51)

5.4.3 Within group analyses

Table 5.4 shows the significant within group activations for all 6 groups of the two analyses and the two ToM contrasts. This table shows that there were many significant activations elicited in the temporal regions, as well as in non hypothesized regions such as the fusiform, cerebellum and precuneus. In the ToM vs Phy contrast the most activation occurred in the lateral temporal regions (superior and middle temporal gyri) and precuneus in all groups, with seemingly little frontal activation at the used threshold (P=0.005, 20 voxel cluster extent). Similarly in the ToM vs Jumbled contrast, the majority of activations were observed in the temporal lobes; however there was more frontal activation in the groups than in the ToM vs Phy contrast.

Table 5.4 Significant within group activations for both ToM vs Phy and ToM vs Con contrasts.

Condition & Group	*P*	*Extent*	*Z*	*Peak height (x,y,z)*	*Region*
ToM vs Phy					
HR-	P<0.0001	915	4.53	10 -50 50	Right Precuneus BA7
	P<0.0001	1285	4.48	55 -66 11	Right Middle Temporal Gyrus BA39
	P<0.0001	673	3.94	-59 -57 18	Left Superior Temporal Gyrus BA22 (TPJ)
HR+	P<0.0001	1801	5.05	61 -54 8	Right Middle Temporal Gyrus BA22
	P<0.0001	1487	4.30	4 -58 49	Right Precuneus BA7
	P<0.0001	1023	4.21	-59 -58 5	Left Middle Temporal Gyrus BA37
Controls	P<0.0001	1403	5.10	-6 -48 45	Left Precuneus BA7
	P<0.0001	1306	4.15	51 -41 30	Right Inferior Parietal Lobule BA40
	P=0.002	395	3.79	-59 -56 8	Left Middle Temporal Gyrus BA21
HR+Now	P<0.0001	583	4.46	46 -42 21	Right Superior Temporal Gyrus BA22 (TPJ)
	P<0.0001	473	4.20	-2 -50 49	Left Precuneus BA7
	P<0.0001	208	4.09	-62 -56 1	Left Middle Temporal Gyrus BA37
	P=0.001	124	4.01	-36 -74 28	Left BA19 Superior Occipital Gyrus
	P<0.0001	134	3.87	-48 -69 20	Left Middle Temporal Gyrus BA39
	P=0.048	67	3.36	53 -70 3	Right Inferior Temporal Gyrus BA37
HR+Ever	P=0.002	135	4.05	57 -60 12	Right Middle Temporal Gyrus BA37
	P=0.003	125	3.39	-4 -63 14	Left Precuneus BA31
HRill	P=0.008	46	3.46	63 -37 2	Right Middle Temporal Gyrus BA21
ToM vs Jumbled Images					
HR-	P<0.0001	1146	4.19	-10 -61 60	Left Precuneus BA7
	P<0.0001	2938	5.01	-53 -64 0	Left Inferior Temporal Gyrus BA37 Occipital Lobe
	P=0.007	338	4.59	4 63 21	Right anterior Frontal Cortex BA10
	P<0.0001	1008	4.36	51 29 4	Right Inferior Frontal Cortex BA 45
	P<0.0001	2245	4.30	50 -71 15	Right Middle Temporal Gyrus BA39 (TPJ)
	P<0.0001	518	4.28	-55 27 2	Left Inferior Frontal Gyrus BA45
	P<0.0001	608	3.96	55 -5 -27	Right Inferior Temporal Gyrus BA20
	P=0.014	300	3.78	-53 -5 -23	Left Inferior Temporal Gyrus BA21
HR+	P<0.0001	3761	5.71	46 -54 3	Right BA37

	P<0.0001	3257	5.62	-36 -79 21	Left Middle Occipital Gyrus BA19
	P=0.001	428	4.66	57 -20 -12	Right Middle Temporal Gyrus BA21
	P=0.013	287	4.31	-26 -40 -15	Left Cerebellum
	P=0.003	365	4.17	36 11 27	Right Frontal lobe BA8
	P<0.0001	677	3.62	10 -57 64	Right Precuneus BA7
Controls	P<0.0001	3104	5.43	-57 -61 18	Left Superior Temporal Gyrus BA39 (TPJ)
	P<0.0001	785	5.01	0 -56 47	Left Precuneus BA 7
	P<0.0001	3191	4.78	50 -70 15	Right Middle Occipital Gyrus BA39
	P=0.004	389	4.57	4 56 34	Right Superior Frontal Gyrus BA9
	P<0.0001	535	4.08	57 24 14	Right Inferior Frontal Gyrus BA 45
HR+Now	P<0.0001	1756	4.39	40 -54 10	Right Middle Temporal Gyrus BA21
	P<0.0001	1277	4.04	-46 -71 24	Left Superior Occipital Gyrus BA39/19
HR+Ever	P<0.0001	1599	5.14	51 -63 -9	Right BA 37 Inferior Temporal Gyrus
	P<0.0001	1975	4.84	-46 -73 15	Left Middle Occipital Gyrus BA19
	P=0.001	164	4.18	51 -10 -15	Right Middle Temporal Gyrus BA21
	P=0.001	177	4.16	-22 -5 -22	Left Amygdala
	P=0.041	99	4.04	6 -60 47	Right Precuneus BA7
	P=0.024	109	3.80	-16 -47 -40	Left Cerebellum
	P<0.0001	207	3.66	-28 -40 -15	Left Fusiform Gyrus BA 36
HRill	P<0.0001	120	4.56	-36 13 -19	Left Temporal Lobe BA38
	P=0.006	61	4.50	-50 -46 13	Left STS/STG BA22
	P<0.0001	228	4.46	-4 57 17	Left MPFC BA9
	P=0.016	53	3.85	46 -77 8	Right Middle Occipital Gyrus BA19
	P=0.026	49	3.65	55 -16 -16	Right Middle Temporal Gyrus BA21
	P=0.006	60	3.39	10 57 21	Right PFC BA 9

Table 5.5 shows the within group significant activations across the groups for the Physical cartoon versus jumbled image contrast. When this contrast's results were visually compared to the ToM cartoons vs. Jumbled Images contrast results it was found that activations unique to the ToM cartoons were in MPFC (BA 9 and 10), left amygdala and precueus (BA7).

There was a unique activation in the anterior frontal cortex (BA11) in the Physical vs. Jumbled image condition.

Table 5.5 Significant within group activations for Phy vs Con

Condition & Group	*P*	*Extent*	*Z*	*Peak height (x,y,z)*	*Region*
Phy vs Jumbled Images					
HR-	P<0.0001	2434	5.00	-38 -87 3	Left inferior Occipital Gyrus BA18
	P<0.0001	3159	4.66	-48 -66 -7	Left Inferior Temporal Gyrus BA37
	P<0.0001	436	4.34	-46 27 -13	Left Inferior Frontal Gyrus BA47
	P<0.0001	431	4.29	53 31 -2	Right Inferior Frontal Gyrus BA47
HR+	P<0.0001	5049	5.71	-30 -40 -15	Left Fusiform Gyrus BA36
	P<0.0001	4732	4.98	48 -55 19	Right STG/ STS BA22
	P=0.032	284	4.68	-8 -75 -2	Left Lingual Gyrus BA18
	P<0.0001	722	4.60	46 5 29	Right Precentral Gyrus BA6
	P=0.011	350	4.24	2 -58 -30	Right Cerebellum
Controls	P<0.0001	8040	5.19	-50 -53 -7	Left Inferior Temporal Gyrus BA37
	P=0.001	473	4.32	-50 3 29	Left Precentral Gyrus BA6
	P<0.0001	966	4.24	59 13 23	Right Inferior Frontal Gyrus BA44
	P=0.001	529	3.68	-28 26 -22	Left Inferior Frontal Gyrus BA11
HR+Now	P=0.001	169	4.74	-30 -42 -15	Left Fusiform Gyrus BA36/37
	P<0.0001	268	4.69	12 -77 -28	Right Cerebellum
	P=0.030	105	4.17	-8 -79 -30	Left Cerebellum
	P=0.006	134	4.13	12 -60 -34	Right Cerebellum
	P=0.037	101	4.06	18 -93 -4	Right Sulcus Calcarinus BA17
	P<0.0001	916	3.53	48 -58 12	Right Middle Temporal Gyrus BA37
	P<0.0001	807	3.72	-55 -50 3	Left Middle Temporal Gyrus BA21
HR+Ever	P<0.0001	2094	4.99	-32 -86 25	Left Middle Occipital Gyrus BA18
	P<0.0001	501	4.83	-22 -44 -16	Left Cerebellum
	P<0.0001	439	4.68	51 -65 -9	Right Inferior Temporal Gyrus BA17
	P=0.042	103	4.52	-4 -77 -28	Left Cerebellum
	P<0.0001	583	4.47	40 -69 27	Right BA19
	P=0.028	111	4.28	26 -89 -1	Right Lingual Gyrus BA18
	P<0.0001	216	4.18	32 9 27	Right Inferior Frontal Gyrus BA44
	P=0.016	121	3.37	-51 17 23	Left Inferior Frontal Gyrus BA44
	P<0.0001	172	3.30	32 -47 -11	Right Fusiform Gyrus BA37
HRill	P<0.0001	182	4.03	-44 -2 -30	Left Inferior Temporal Gyrus BA20
	P<0.0001	263	4.00	-26 -35 -2	Left Hippocampul Gyrus BA30
	P=0.009	64	3.92	42 29 -12	Right Inferior Frontal Gyrus BA47
	P=0.005	70	3.85	-50 10 12	Left Inferior Frontal Gyrus BA44
	P<0.0001	102	3.78	24 -89 10	Right Medial Occipital Gyrus BA18
	P<0.0001	133	3.67	-14 -86 -6	Left BA18
	P=0.005	69	3.56	-10 -22 -12	Left Pulvinar

5.4.4 Within group Maximum Intensity Projections (MIP's)

The significant between group activations for the ToM vs Phy & Con contrast can be viewed in Table 3 in the appendix.

The within group MIP's for the ToM vs Phy and ToM vs Con contrast and their respective inverse contrasts (Phy vs ToM and Con vs ToM) are detailed below for both analyses. The MIP's show the activation clusters detailed in the above tables.

The ToM vs Phy & Con and the Phy vs Con within group MIP's can be viewed in the Appendix.

For all MIP's, statistical maps were thresholded at a level of P=0.005 uncorrected voxel level and regions were considered significant at P<0.05 cluster level corrected for multiple comparisons.

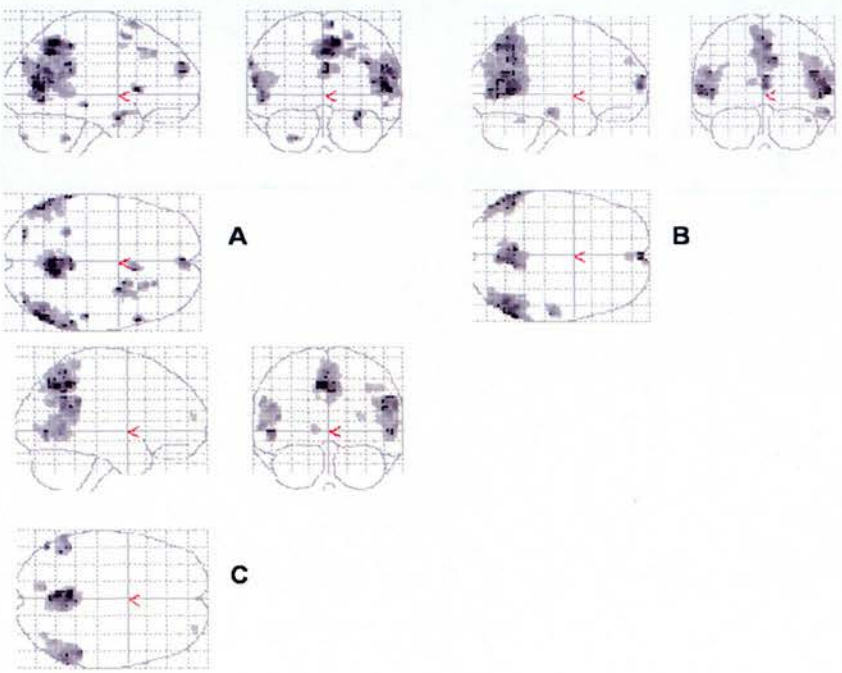


Figure 5.2 ToM vs Phy contrast Maximum Intensity Projection image for Analysis 1 groups. Where A=HR-, B=HR+, C=Controls.

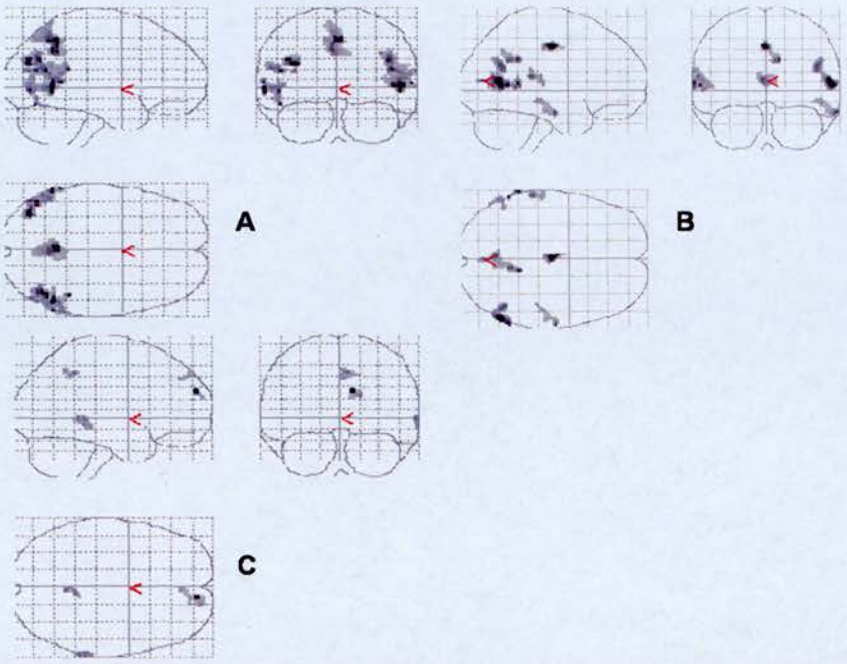


Figure 5.3 ToM vs Phy contrast Maximum Intensity Projection image for Analysis 2 groups. Where A=HR+Now, B=HR+Ever, C=HRill.

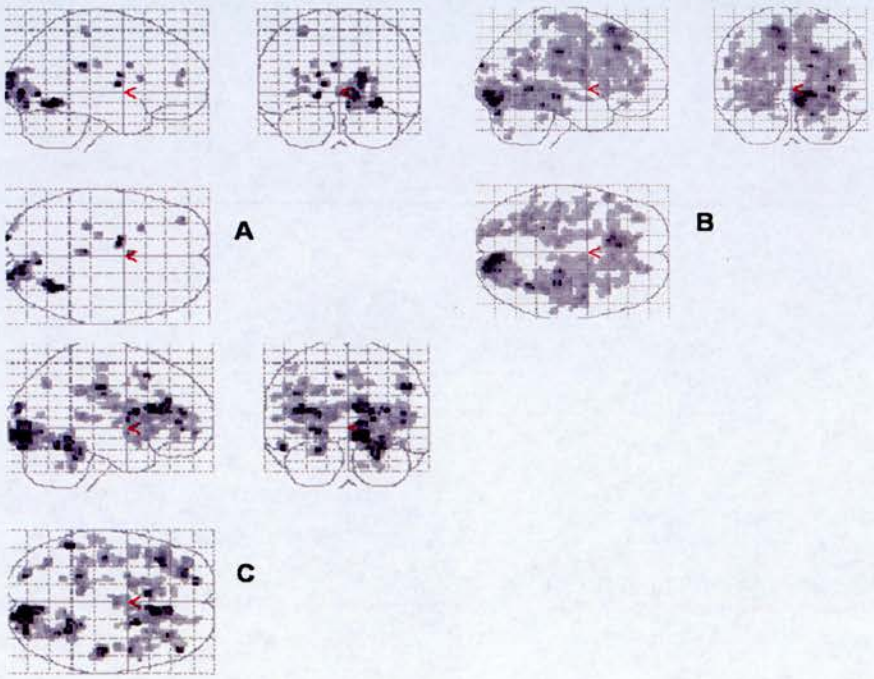


Figure 5.4 Phy vs ToM contrast Maximum Intensity Projection image for Analysis 1 groups. Where A=HR-, B=HR+, C=Controls.

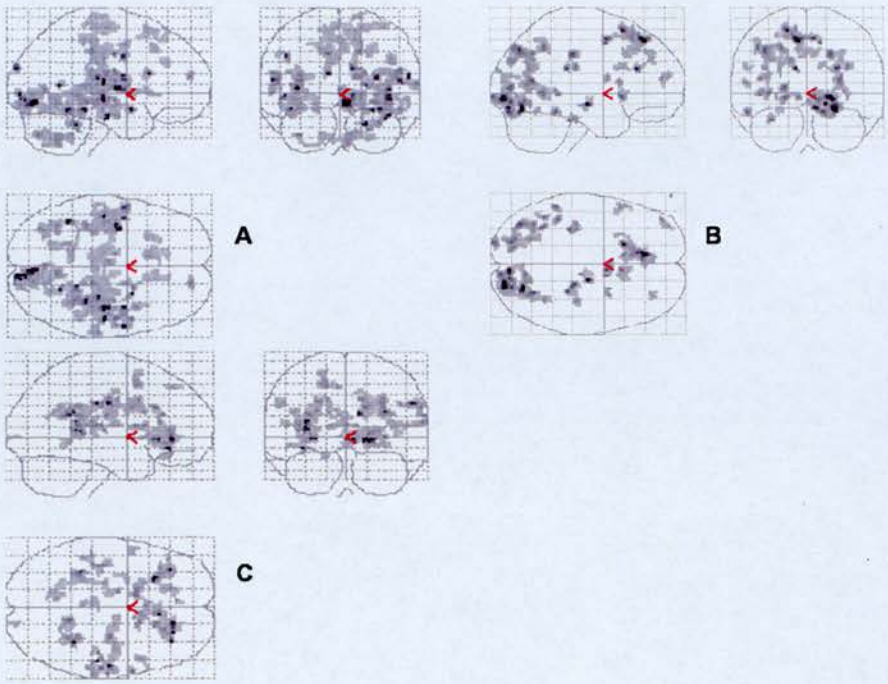


Figure 5.5 Phy vs ToM contrast Maximum Intensity Projection image for Analysis 2 groups. Where A=HR+Now, B=HR+Ever, C=HRill.

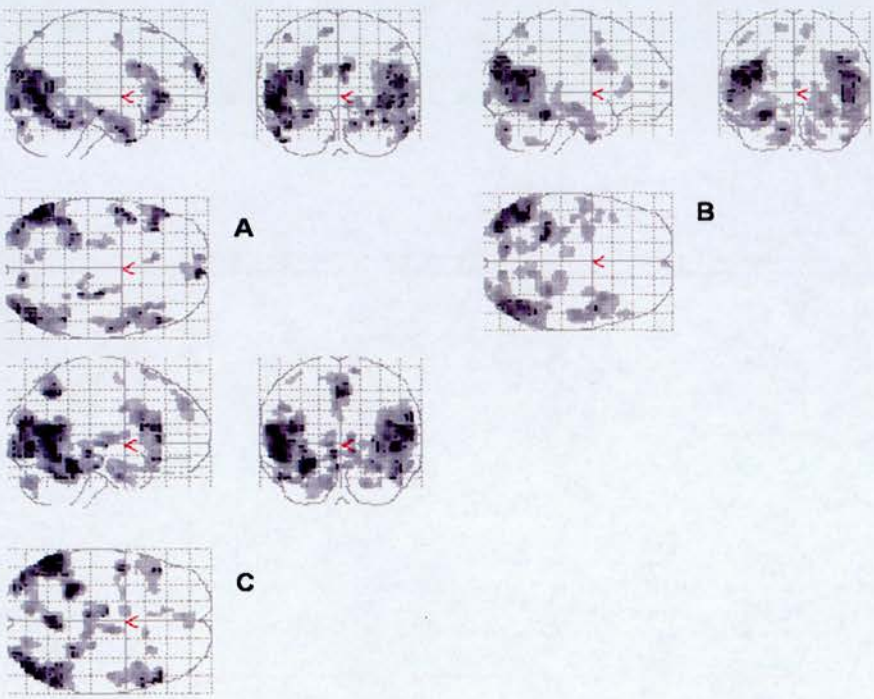


Figure 5.6 ToM vs Con contrast Maximum Intensity Projection image for Analysis 1 groups. Where A=HR-, B=HR+, C=Controls.

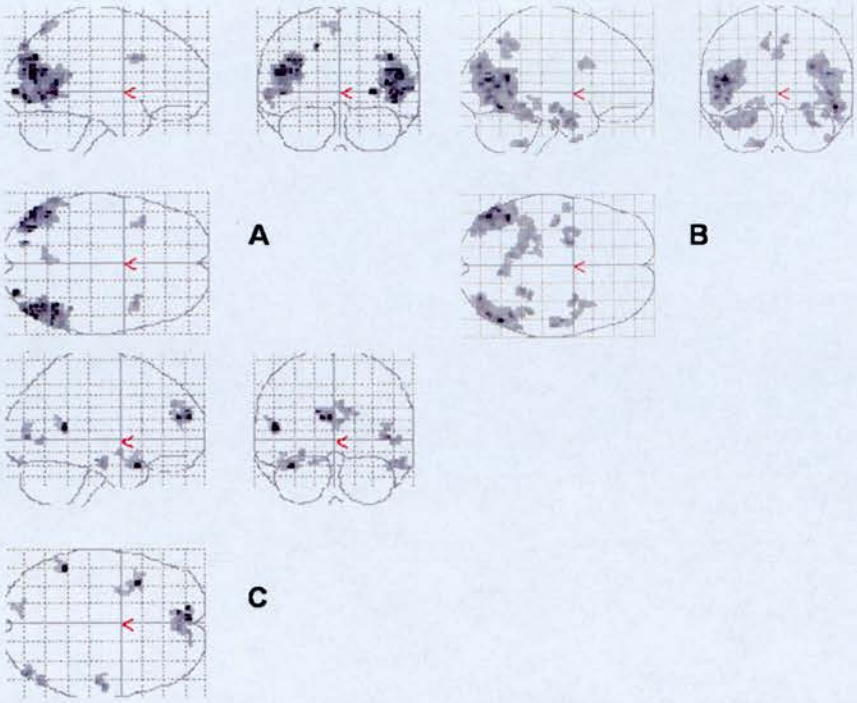


Figure 5.7 ToM vs Con contrast Maximum Intensity Projection image for Analysis 2 groups. Where A=HR+Now, B=HR+Ever, C=HRill.

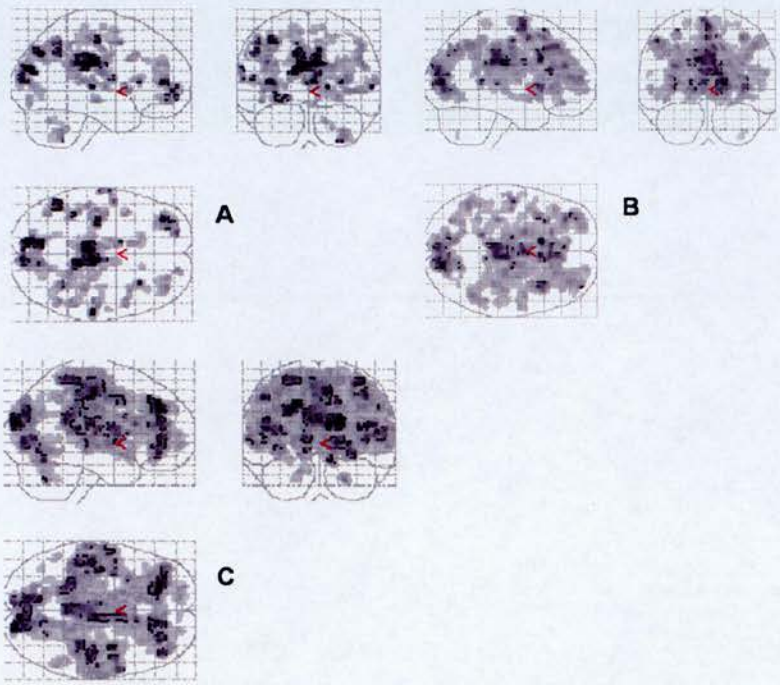


Figure 5.8 Con vs ToM contrast Maximum Intensity Projection image for Analysis 1 groups. Where A=HR-, B=HR+, C=Controls.

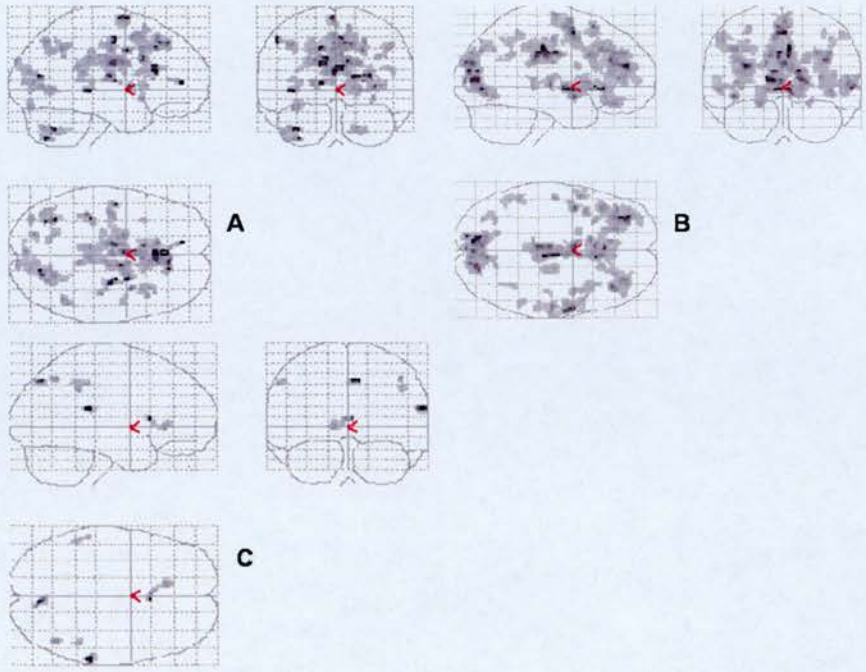


Figure 5.9 Con vs ToM contrast Maximum Intensity Projection image for Analysis 2 groups. Where A=HR+Now, B=HR+Ever, C=HRill.

5.4.5 Between group analyses

5.4.5.1 Analysis 1

In the ToM vs. Phy cartoon condition; there were significant activation differences between the HR- and HR+, as detailed in Table 5.6. The former activated significantly greater than the latter in the right precuneus, bilateral medial frontal gyrus and left MPFC. Trends were evident for greater activation in the right insula, left inferior frontal gyrus and left temporal lobe, in the HR- relative to HR+. Crucially, there were no significant differences between the controls and the HR groups.

In the ToM vs. Con images contrast, there was significant group differences in the left motor and supplementary motor regions with the HR+ groups activating

significantly greater than the controls in these regions. The HR- activated significantly greater than the HR+ in the left fusiform.

Table 5.6 Analysis 1 Between Group Differences

Condition & Group	*P*	*Extent*	*Z*	*Peak height (x,y,z)*	*Region*
ToM vs Phy Images					
HR->HR+	0.001	698	4.34	32 -40 37	Right BA7
	<0.0001	953	4.12	-14 -21 45	Left BA6 Middle Frontal Gyrus
	0.006	494	3.71	-20 7 29	Left BA8
	0.019	398	3.48	26 12 40	Right BA6 Middle Frontal Gyrus
ToM vs Con Images					
HR+>Con	0.031	411	4.06	-48 -19 41	Left Post central gyrus BA1
	0.039	392	4.04	-50 -20 18	Left BA2
HR->HR+	0.020	449	3.73	-30 21 -9	Left Fusiform

5.4.5.2 Analysis 2

In the ToM vs. Phy cartoon condition the HR+Ever activated significantly greater than the HR+Now in right BA9 and fusiform and greater than the HRill in right BA8. The HR+Now acitivated greater than the HR+Ever also in right BA9, but in a more ventral region.

In the ToM vs. Con images contrast, the HRill group activated significantly greater in left BA8 than the HR+ group as a whole and the HR+Ever group. The HR+Now group activated significantly greater than the HRill group in left BA19 whilst the HR+Ever group activated significantly greater than the HRill in the right precuneus. These results are displayed in Table 5.7.

Table 5.7 Analysis 2 Between Group Differences

Condition & Group	*P*	*Extent*	*Z*	*Peak height (x,y,z)*	*Region*
ToM vs Phy Images					
HR+Now>HR+Ever	0.034	197	3.95	34 48 18	Right BA9/46 Middle Frontal Gyrus
HR+Ever>HR+Now	0.018	223	4.24	34 25 32	Right BA8 Middle Frontal Gyrus
	<0.0001	390	4.22	36 -49 -14	Right Fusiform Gyrus BA37
HR+Ever>HRill	0.040	191	4.02	26 17 34	Right BA8 Middle Frontal Gyrus
ToM vs Con Images					
HRill>HR+	0.009	310	4.84	-6 22 43	Left Inferior BA8
HR+Now>HRill	0.014	248	4.08	-36 -70 33	Left BA19
HR+Ever>HRill	0.047	227	3.83	14 -52 45	Right Precuneus BA7
HRill>HR+Ever	0.009	310	5.00	-6 22 48	Left BA8

5.4.5.3 Analysis 3

In order to investigate the observed between group PFC activation differences further, particularly BA8 activity, an exploratory post hoc analysis was conducted that compared all the groups from analyses 1 and 2 to each other. The first two analyses investigated trait and state via the comparison of balanced sized groups. This post hoc analysis compared the smaller groups of analysis 2 with the larger groups of analysis 1, hence the HR- and controls were compared to the HR+Now, HR+Ever and the HRill groups of analysis 2. The observed group differences were between the HR- and both the HR+Now and HRill groups. There was significantly greater activation in the HR- in bilateral BA8, right fusiform, left tempero-parietal junction and left cerebellum, when this group was compared to the HR+Now. The HR- were also found to activate significantly greater than the HRill in right posterior cingulate/paracentral lobule. The significant group differences are detailed in Table 5.8.

Table 5.8 Between HR- and HR+Now and HRill group differences in the post-hoc analyis of ToM vs Phy contrast.

Condition & Group	*P*	*Extent*	*Z*	*Peak height (x,y,z)*	*Region*
HRneg>HR+Now	P<0.0001	1595	4.55	-42 -25 5	Left BA22 TPJ/Superior Temporal Gyrus
	P<0.0001	2890	4.49	10 39 33	Right BA8 Medial Frontal Gyrus
	0.002	608	4.03	-14 27 32	Left BA8/32 (medial/anterior cingulate)
	0.005	503	3.72	-12 -66 -29	Left posterior lobe, Cerebellum
HRneg>HRill	0.030	362	3.53	18 -25 36	Right Cingulate/Paracentral lobule

5.4.6 Conjunction analysis

Conjunction analyses are used to investigate what is common to a group of individuals and is used with masking. All subjects are entered into the same statistical model but the parameters for each subject are estimated independently in a subject separable design matrix. You then enter contrasts separately for each subject. The conjunction analysis gave the possibility to investigate whether there was any overlap in the concerned BA's of the group's activation clusters in the main ToM vs. Phy contrast. It was found that although groups activated in the same BA region (e.g. BA 8 and 9), in this instance it was observed that the particular individual group clusters were not in the exact same area of these regions.

5.4.7 Contrast Estimates

Activation overlays and contrast estimate graphs at the voxel of maximum intensity for examples of PFC and temporal lobe significant between group differences for the above three between group analyses are shown below.

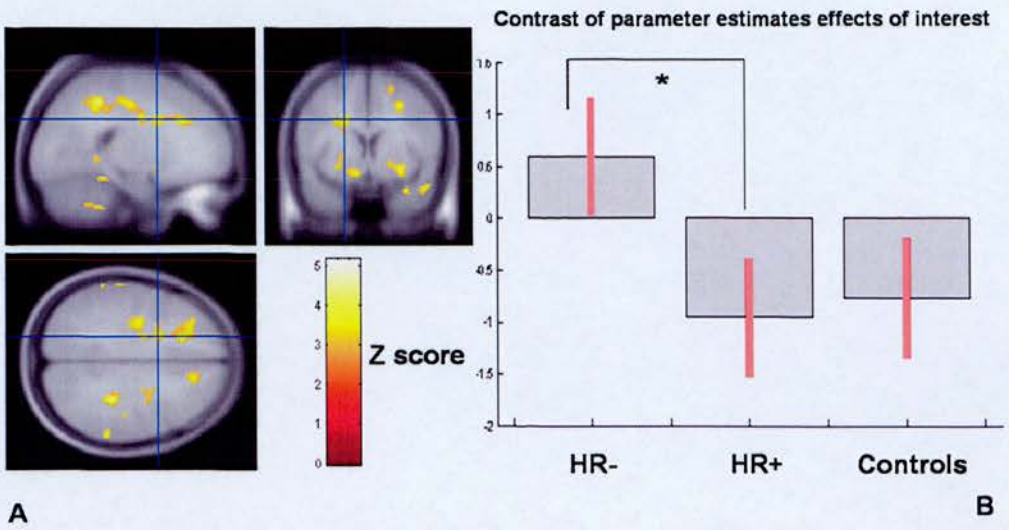


Figure 5.10 ToM cartoons vs. Physical cartoons: between-group differences. (A) **Group comparison showing relatively greater activation in middle PFC (BA8) in high-risk subjects without psychotic symptoms versus high-risk subjects with psychotic symptoms and controls. Maps thresholded at P<0.005 uncorrected voxel level, extent threshold 20 voxels. Blue crosshairs are placed in voxel of maximum difference within significant clusters.** (B) **Effect size at peak co-ordinate [-20, 7, 29]. * = significantly different.**

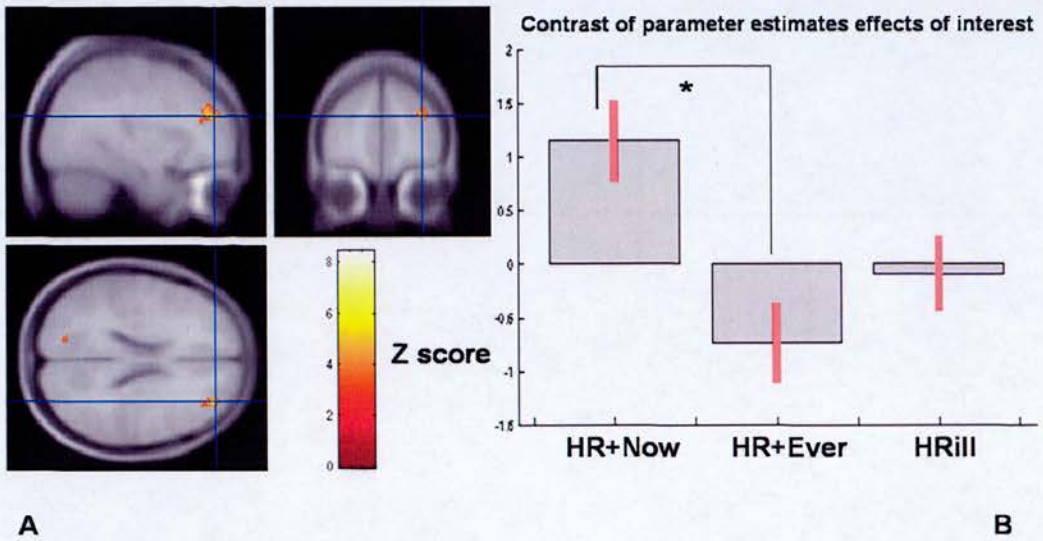


Figure 5.11 ToM cartoons vs. Physical cartoons: between-group differences. (A) Group comparison showing relatively greater activation in middle PFC (BA9) in HR+Now versus HR+Ever subjects. Maps thresholded at P<0.005 uncorrected voxel level, extent threshold 20 voxels. Blue crosshairs are placed in voxel of maximum difference within significant clusters. (B) Effect size at peak co-ordinate [34, 48, 18]. * = significantly different.

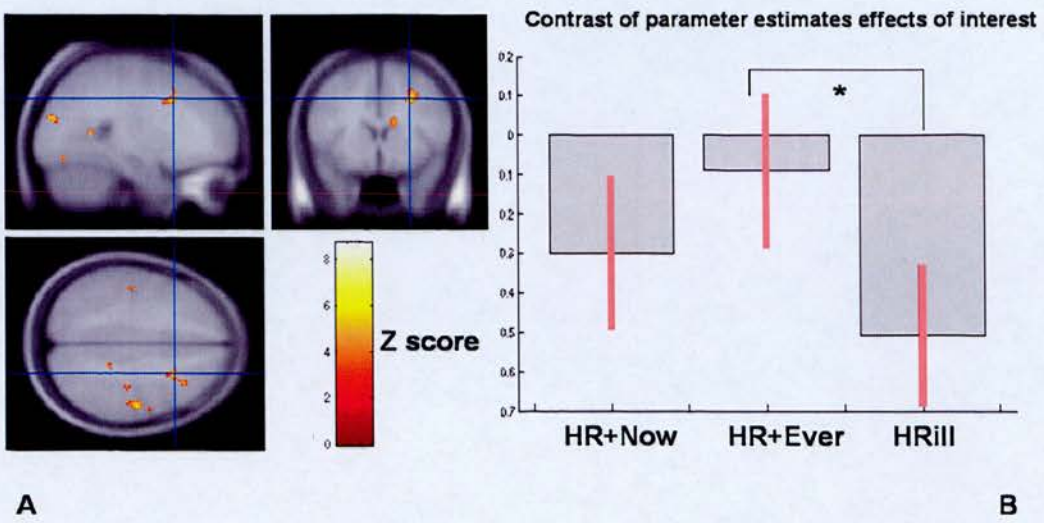


Figure 5.12 ToM cartoons vs. Physical cartoons: between-group differences. (A) Group comparison showing relatively greater activation in middle PFC (BA8) in HR+Ever versus HRill subjects. Maps thresholded at P<0.005 uncorrected voxel level, extent threshold 20 voxels. Blue crosshairs are placed in voxel of maximum difference within significant clusters. (B) Effect size at peak co-ordinate [26, 17, 34]. * = significantly different.

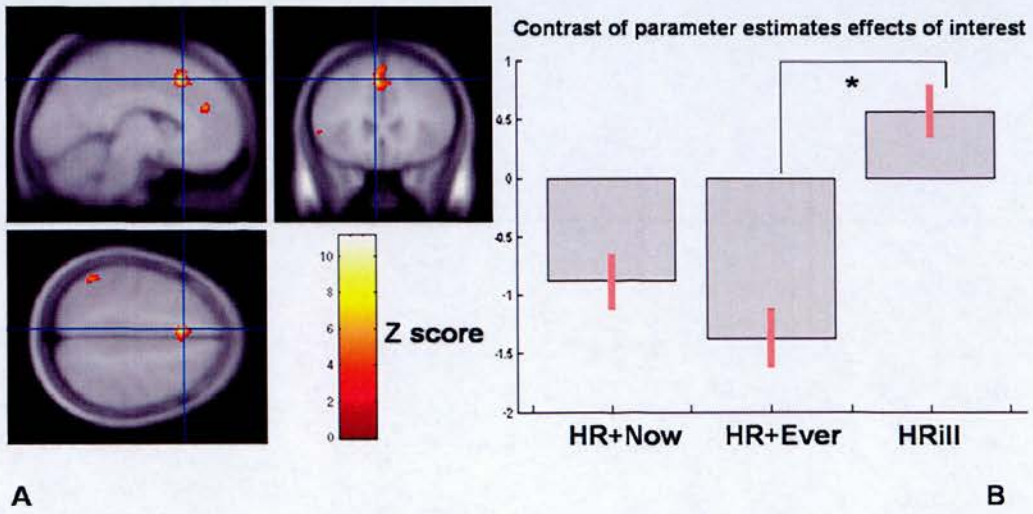


Figure 5.13 ToM cartoons vs Control images: between-group differences [Analysis 2, Table 7]. (A) Group comparison showing relatively greater activation in MPFC (BA8) in HRill versus HR+Now subjects. Maps thresholded at P<0.005 uncorrected voxel level, extent threshold 20 voxels. Blue crosshairs are placed in voxel of maximum difference within significant clusters. (B) Effect size at peak co-ordinate [-6, 22, 48]. * = significantly different.

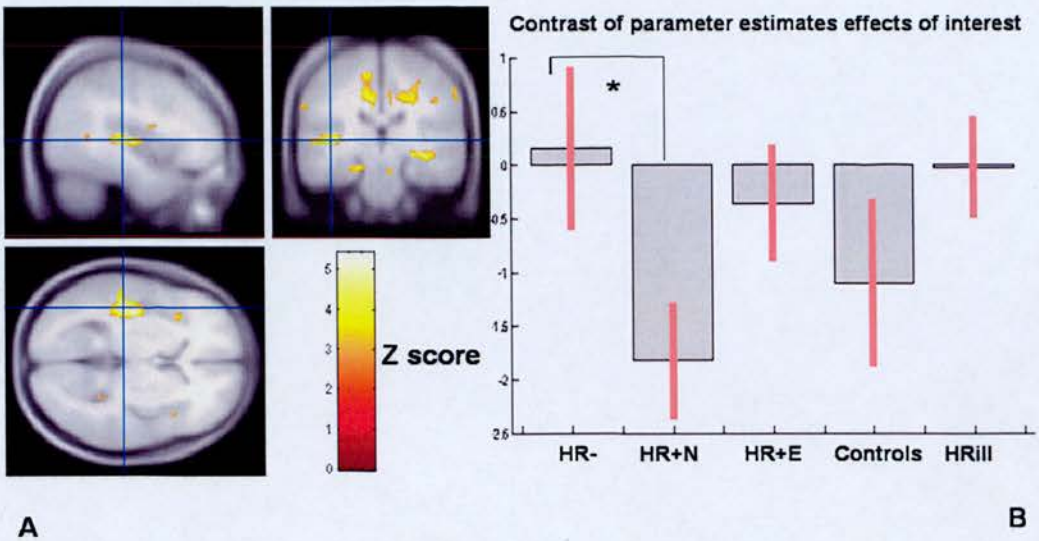


Figure 5.14 ToM cartoons vs Physical cartoons: between group differences [Analysis 3, Table 8]. (A) **Group comparison showing relatively greater activation in BA22 in high-risk subjects without psychotic symptoms, high risk subjects with psychotic symptoms and controls. Maps thresholded at P<0.005 uncorrected voxel level, extent threshold 20 voxels. Blue crosshairs are placed in voxel of maximum difference within significant clusters.** (B) **Effect size at peak co-ordinate [-42, -25, 5]. * = significantly different.**

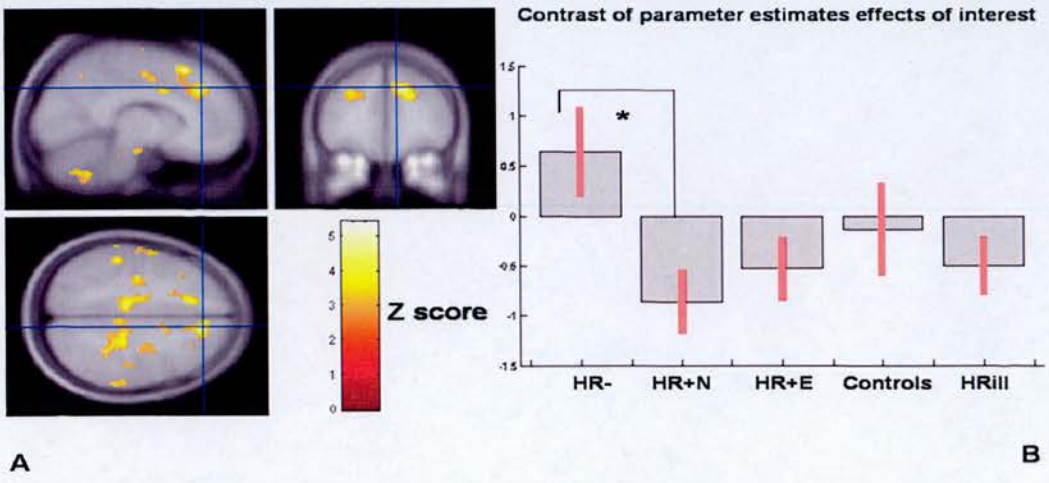


Figure 5.15 ToM cartoons vs Physical cartoons: between group differences [Analysis 3, Table 8]. (A) **Group comparison showing relatively greater activation in MPFC (BA8) in high-risk subjects without psychotic symptoms vs. high risk groups with symptoms and HRill. Maps thresholded at P<0.005 uncorrected voxel level, extent threshold 20 voxels. Blue crosshairs are placed in voxel of maximum difference within significant clusters.** (B) **Effect size at peak co-ordinate [10, 39, 22]. * = significantly different.**

5.5 Discussion

This imaging study aimed to investigate possible impairment of the neural circuits supporting mentalising capabilities in individuals at enhanced risk of schizophrenia. We investigated possible state/trait effects using two analyses. In analysis 1, state and trait effects were investigated by comparing the HR group as two groups split on symptoms, HR+ and HR-, against the control group. In analysis 2, we compared state effects by splitting the HR+ group on the basis of previous and current psychotic symptoms and comparing them both to each other and with a group of HR individuals who had gone on to develop schizophrenia. In a third exploratory post hoc analysis we further investigated state and trait by comparing the activations of the HR+Now and HR+Ever groups against the HR- and control groups.

5.5.1 Behavioural data

5.5.1.1 Analysis 1

There was no significant group difference in reaction times of button pressing to the stimuli. Each group was slightly quicker in pressing the button in the Physical cartoon conditions than the ToM cartoon conditions, although this difference was not significant. This difference is to be expected as the ToM cartoons by their nature conveyed more information than their Physical "slapstick" counterparts. The control group was faster at button pressing in the Jumbled image condition than the two HR groups but again this difference was not significant.

There were no significant group differences for Physical joke debrief scores. There were two ToM debrief scores: ToM 1 was for correctly describing the jokes whilst ToM 2 only took account of the responses which used mentalising language in the joke description (e.g. he is *unaware* that, they do not *realize* that, she *thinks* that they are, etc). There were no significant group differences on these two scores but the ToM 2 score was significantly lower than the ToM 1 score for all groups.

5.5.1.2 Analysis 2

The HR+Ever were consistently quicker than both the HR+Now group and the HRill group at button pressing in the three conditions. This difference was significant in the Jumbled image and ToM cartoon conditions. The HRill were quicker at button pressing than the HR+Now group in the Jumbled Image and Physical cartoon condition images, although not to a significant extent.

There were no significant group differences for ToM 1 debrief scores but there was a significant group difference on the ToM 2 score with the HRill performing significantly worse than the HR+Now. Similarly to analysis 1, all groups debrief ToM 2 score was significantly lower than their ToM 1 score.

It is apparent that there is a large difference between all groups two ToM debrief scores. All groups went from a double figure score to a single figure score. The lack of incorporation of mentalising language in a seemingly correct description of the joke does not necessarily represent a failure of mentalising ability but rather a failure of verbalization. As described below, the ToM jokes elicited activation in key hypothesized regions associated with mentalising abilities. The neural correlates of the task therefore suggest that a ToM and social cognition circuit was engaged to varying degrees by participants, implying that they were getting the majority of the

jokes in mentalisitic terms. The HRill having a significantly poorer score on the ToM2 debrief score is in fitting with the literature for a verbalization deficit in individuals with schizophrenia (e.g. (103) and discussed in the discussion of the pilot study, chapter 4). As both the HR groups score similarly to the controls then poor verbalization skills on this task appear not to be trait related. It appears that all groups were not explicitly verbalizing their implicit mentalising adequately when describing the ToM jokes.

5.5.2 Within Group activations

The pictorial visual joke task employed elicited robust activations across the groups both within two of the three a priori hypothesised regions and regions consistently activated in the literature (see reviews by (17,23,24,26,96,221). There will follow a succinct summary of the regions in which we found significant activation across the groups in the two analyses.

5.5.2.1 Precuneus

This brain region has been consistently activated in previous mentalising imaging studies. The precuneus has been implicated in a range of studies investigating intentions to act and thinking about one's own intentions (216). It has also been activated in tasks that involve identifying the words that describe oneself, retrieval of autobiographical memories, engaging in self-generated actions and self-monitoring and discriminating between ToM and physical stories (246).

The activation observed in this pictorial paradigm is likely therefore to have been due to it's involvement in the discrimination between ToM and physical visual jokes.

5.5.2.2 Inferior Parietal Lobule

This heteromodal association cortical region, approximately BA's 39 and 40, has been implicated in the pathophysiology of schizophrenia. These neuropsychological deficits are associated with problems in attention, perception, affect recognition and visuospatial processing. The left side is believed to be lateralised for cognitive tasks related to perception and visuospatial processing (247). The majority of the activation in this brain region occurred in the ToM vs. Phy contrast of this task.

In previous EHRS fMRI studies significant between group differences have been observed in this region. On both an episodic memory task (169) and the Hayling sentence completion task (139), the HR+ group was found to activate greater in this region than both the HR- group and controls.

5.5.2.3 Cerebellum

The cerebellum was activated bilaterally on many occasions across the groups in the within group analysis and it is likely that it was involved in the control of eye movements, cognition and the movements related to the button pressing. Cerebellum activation is also apparent in tasks that do not involve overt limb movements and this implies that the cerebellum does have a role in cognition. Imaging studies on healthy volunteers have implicated the cerebellum in tasks of verbal working memory, attention, sensory processing, memory retrieval and language (81). The cerebellum is

believed by some to have a role in the psychopathology of schizophrenia. Andreasen (248) proposes that the basic deficit in schizophrenia is a failure in the process of monitoring and coordination of cognition or 'cognitive dysmetria' due to a dysfunctional fronto-cerebellar network (see also (249)). Furthermore, the cerebellum has also been associated to a varying degree with the perception, control and execution of laughter (226,250).

5.5.2.4 Prefrontal Cortex

The PFC is the major arena of higher cognitive functions and it is of no surprise that it is consistently activated in all mentalising imaging tasks, regardless of the modality used. This was one of our key a priori regions and our activations are in agreement with the literature, (see for example, (23,219,251-253). We obtained bilateral activations across the groups in middle and medial PFC. The PFC also has direct connection to other areas activated in mentalising tasks, the temporal poles and other regions of the temporal lobes via the arcuate and uncinate fasiculi.

The important role of the PFC in mentalising abilities has further been shown by both lesion and other frontal damage studies showing compromised mentalising ability in these affected individuals (254-257). These and similar studies can be viewed in Table 2 in the Appendix. Of particular interest is a recent study in which an individual with extensive PFC damage (due to bilateral cerebral artery infarction) was tested on a very extensive battery of ToM neuropsychological tasks and found to perform within the normal range on all except one aspect of one task (258). Whether this is a fascinating example of extreme neural plasticity or evidence that the PFC is not as important in mentalising ability as a large number of studies imply, cannot be

adequately answered on the basis of investigation into a single person and replication in a group of patients with the same injury is required.

5.5.2.5 Temporal Lobes

The temporal lobes comprise a large brain region and ToM imaging tasks elicit activation in several distinct areas. We also observed activations in several distinct regions of these lobes:

5.5.2.5.1 Superior Temporal Sulcus

The STS has been consistently activated in numerous mentalising studies, regardless of the employed modality. Gallagher et al., (197) found the right sided STS to be associated with understanding the meaning of cartoons and stories involving people, with and without the requirement to mentalise. The STS is also believed to be involved in the perception of biological motion (259). Biological motion contains information about the identity of the moving stimulus, his or her actions, intentions and even emotions. A deficit in biological motion perception could have a wide range of consequences for social perception and interpersonal functioning (260).

It has been suggested that the ability to mentalise may have evolved from the ability to detect the motion of animate agents and to then subsequently infer intentions from actions (219,220).

Other ToM tasks that elicit STS activations include understanding causality and intentionality, attribution of intentions to moving shapes (196,203), the taking of the self-perspective (221) and pictorial tasks involving empathy (49).

In a previous EHRS fMRI study (81), the HRall and HR+ groups showed a non significant increased response than the controls in the right middle temporal gyrus (BA20 & 21). The right middle temporal lobe is believed to be involved in auditory visual hallucinations in schizophrenia (261). It has also been implicated in verbal self-monitoring in schizophrenia and the disruption of this region is believed to be key in the development of auditory hallucinations (262,263).

5.5.2.5.2 Temporal-Parietal Junction (TPJ)

The TPJ (approximately the ventral portions of BA41, 21, 22 and their borders with the dorsal aspects of BA 40 and 39*),* has been shown to be activated in relation to biological motion and to stimuli which signal intentions and intentional activity (197,264). This region has also been activated in tasks requiring participants to mentalise about other people (207,265), although there is debate as to whether activation in this region is specific to ToM abilities per se as some studies have found activation in the non-theory of mind conditions of the employed fMRI paradigm (e.g. (191,197).

5.5.2.5.3 Superior Temporal Gyrus

Previous imaging studies have shown activation in the STG which increases when participants attend to the more "socially relevant" dimensions of a visual display, such as emotion, trustworthiness, and contingency between inanimate objects (264).

5.5.2.5.4 Temporal poles

This region has been found to be activated in association with semantic knowledge and decoding (266) and with episodic memory retrieval in the auditory and visual domains (see (221), for an interesting discussion on how episodic memory may be important for mentalising capabilities) and it may hold memories for social scripts (26). These are required for access to social knowledge to aid interpretation of social situations. We obtained one significant within group activation in this region and it could be that the appreciation of visual jokes does not require these episodic memories of social scripts, or the requirement of participants to draw on past experiences and their related emotional information to the extent of other ToM paradigms, particularly verbal stories. It has been suggested that the temporal pole is concerned with generating, on the basis of past experiences, a wider semantic context for the material currently being processed. The temporal pole constitutes a component of the paralimbic cortex which has putative functions that include imparting affective tone to experience. This was reported to activate during both the incidental retrieval of emotional contextual information in single word recognition and during the retrieval of previously studied emotional pictorial materials in comparison with the retrieval of neutral materials. This implies that the temporal poles have an important role in the retrieval of emotional and semantic information (218). The temporal poles have also been implicated in the comprehension of humour (226).

5.5.2.6 Amygdala and Fusiform gyrus

The amgydala plays a large role in social cognition and is known to be responsive to eye gaze and emotional content of faces (194,226,267). Bilateral activation was

observed in the fusiform which is associated with the processing of faces and objects (196,197) and these activations in these two regions are in fitting with the pictorial nature of the task.

5.5.3 Between group analyses

The vast majority of significant between group activation differences were observed in the PFC. In the first between group analysis we investigated trait and state by comparing the HR- and HR+ groups both against each other and the control group. In the ToM vs. Physical cartoon contrast, it was found that the HR- activated significantly greater than the HR+ in the inferior parietal lobule and several regions of the Prefrontal cortex. This contrast is the most interesting as activations allegedly involved in mentalising will remain when those for the Physical cartoons have been subtracted out. In the same contrast in analysis 2, there was significant PFC (BA8 and 9) activation differences between the HR+ groups and the HRill. Similarly, in the post hoc analysis 3, there were significant PFC activation differences between the HR- and the HR+Now group.

In the ToM vs. Control contrast the significant between group activations for analysis 1 were in the motor and supplementary motor regions. However, in analysis 2, the significant between group activations were in PFC, BA8 (HRill > than HR+, HR+Ever) and the parietal lobe.

5.5.4 Prefrontal cortex revisited

Imaging investigations into schizophrenia have revealed PFC dysfunction and pathology. Schizophrenia patients have been shown to have deficits in smooth

pursuit eye movements (268) and to have deficits in the above executive function domains. Structural imaging studies have found evidence of pathology of PFC, including dilated prefrontal sulci and diminished frontal lobe volume (269). Functional imaging has revealed evidence for both hypo and hyper-frontality in this brain region on numerous executive function based tasks (270). ToM imaging studies have implicated BA8 and 9 as the major PFC regions involved in ToM processing (e.g. (191,192)). In the original study on which this present imaging paradigm is based, Gallagher et al., (197) found that the observed PFC activation was restricted to BA8 in the cartoon condition.

BA8 has been shown to be consistently activated in memory (271) and executive functioning tasks such as decision making (272) and deontic reasoning (273). It has also been linked with the learning of conditional discrimination tasks in non-human primates (of the form, if A, then B, (274)) and some believe that many ToM tasks embody similar reasoning (e.g. (275)). BA9 has been shown to be actively involved in working memory and episodic long term memory (276,277) and decision making (278). Damage to the PFC has been shown to produce deficits in judgement making, planning, decision making, short term memory and behavioural inhibition (279).

High risk studies have found evidence for prefrontal differences in their relative groups, of both a hyper and hypo-frontal nature. Whalley et al., (139) found that increased activity in BA8 was associated with increased genetic risk for the disease. Callicott et al., (240), using a N-back working memory task, showed unaffected siblings exhibited an exaggerated response in the same region, when compared to a control group, in absence of performance differences. Keshavan et al., (239), using a memory guided saccade task, showed that unaffected siblings demonstrated task

related reductions of activity in dorsolateral prefrontal cortex (this was a pilot study and the consequent group numbers were small).

In a non HR study, Russell et al., (198) in an fMRI paradigm, compared the performance of a schizophrenia group against matched controls on the 'Eyes' task. They found that the schizophrenia group had significantly less activation in left middle and inferior PFC (BA9, 44 and 45) and made more errors.

It has become increasingly clear that whether one finds reduced or increased activation on fMRI studies is fundamentally influenced by whether or not subjects can do the task in question (270). The debrief scores, behavioural data and within group activation MIP's all indicate that the participants were performing this task appropriately in the scanner.

Several reasons have been proposed for why PFC activations within this clinical group are different when compared to controls. Schizophrenics could be more variable and less efficient in their use of strategies to accomplish the task; furthermore the increased activation could represent cortical inefficiency or the recruitment of compensatory neural circuitry (270).

5.5.5 Autism ToM imaging studies and PFC

In a PET study, Happe et al., (193) compared the performance of an Aspergers group to controls on a verbal story paradigm (191) and found increased activation in the control group in BA8 in the ToM condition. There was no BA8 activation in the Asperger group but left MPFC (BA9) activation. Baron-Cohen et al., (194) used an fMRI paradigm of the Eyes task to compare activations of an autism group and a matched control group. The controls were found to activate in left dorsolateral (BA

44, 45, 46), and left medial PFC (BA9). The autism group activated less in these frontal regions.

Castelli et al., (203), also using PET, used an animated shape paradigm to investigate activations between a mixed autism/aspergers group and a control group. In the ToM condition, the control group had greater MPFC (BA9) activation relative to the autism group. These studies show between group differences in PFC activations on different ToM tasks in similar regions to the observed significant differences in the PFC in this study. These results further show that BA8 and BA9 are consistently activated in healthy individuals in ToM tasks, regardless of the modality, and further imply that they are integral components of the PFC aspect of a mentalising circuit. The observed under activation in the PFC, particularly BA9, in the autism groups relative to the control groups could be part of the reason for the observed ToM deficit within this clinical population.

5.5.6 Laterality

It is interesting to note that our frontal activation appeared to be group lateralized. The HR+Ever activations were right BA8 and 9 which is similar to the findings of Brunet et al. (195), whilst the HR- and HRill activations were left BA8, which is similar to the studies of Fletcher et al (191), Goel et al (192) and Happe et al, (193). It is, however, important to note that these studies used different ToM tasks. Sabbagh (280) discusses that the left frontal hemisphere may be important for reasoning about the mental states of others whilst the ability to decode others mental states from observable information may be a skill lateralized to the right hemisphere. It could be that the cartoon depictions of animal and human character interactions could require

both these mentalising capabilities. Alternatively, the attribution of different mental states could be based on separate prefrontal circuits (195).

5.5.7 State effect

When all the between group activations are compared, the majority of observed significant group differences were between the HR groups, with one group activating significantly more than the other (the exception to this was in the ToM vs. Con contrast analysis 1, where the HR+ group activated greater then the control group in motor regions). Contrast estimate plots for these maximal voxels show that in all of these group differences, the control group was activating less than the greater activating HR group and usually the second HR group as well.

Evidence for a trait effect would require the HR- to activate significantly different than the controls. This was the case in a previous EHRS investigation, where the observed medial prefrontal differences were only observed between controls and the HR- rather than the HR+ group (139). This was not evident in the main ToM contrast of ToM vs. Phy. With the group differences being between the HR groups themselves and not the HR groups and the controls, this implies a state effect.

In analysis 2, the HRill and HR+ groups activating in more frontal regions, would also support a state effect, at least akin to a graded (severity) state effect, the difference in activation being due to the experience of symptoms at, or at least relatively close to, the time of testing. Whyte (81) commenting on activation in a previous EHRS fMRI study suggests that there is a continuum of frontal activation within the HR+ group.

5.5.8 Hypothesised reasons for observed Group differences

Fletcher (281) states that the observed abnormal activation in clinical studies of a psychotic state could be attributable to: either the cause of, a consequence of or compensation for, the psychotic symptoms. The HR individuals could possibly have an impaired ToM circuit due to being at enhanced risk for schizophrenia which could therefore require some form of compensation from other brain regions. This could result in activations in different regions and in more pronounced activation in alleged "normal" mentalising regions. The observed response is therefore (from this perspective) compensatory to deficient activation in aspects of the required brain networks to adequately perform the task, or at least attempt to successfully complete the task. It is not that there is a failure or deficit in mentalising ability per se; rather the 'normal' mentalising circuit is compromised. This results in cortical inefficiency in the PFC regions and recruitment of additional 'compensatory' regions. In this way, the observed increase in BOLD response in the frontal regions could be interpreted as a consequence of recruitment of additional cortex for compensatory purposes and of increased processing needed to comprehend the jokes, particularly the ToM ones.

As there was no significant difference on the debrief scores between the groups in analysis 1, this putative compensatory mechanism appears then to be working to a certain extent. There is a different neural network to the controls on task processing but the HR groups derive a correct answer. This recruitment of other brain regions does not seem to affect the reaction time of joke processing, indeed the HR- were slightly quicker than the controls in the two joke conditions whilst the HR+ were quicker in the ToM joke condition.

There could also be evidence for state modulation of trait effects in that positive symptomatology impinges on the effectiveness of this alleged compensation. In the first analysis, the HR- can be seen compensating for this possible trait induced compromised mentalising circuit by recruiting more neural circuitry in the frontal lobe and this is why they activate greater than the HR+. The HR+ group may have passed through an unspecified threshold, or be expressing an extended phenotype due to experiencing psychotic symptoms at some time, and consequently are no longer able to effectively compensate for this deficit and are consequently seen to underactivate relative to their HR- counterparts.

In some cases the HR+ appear to activate similarly to the controls (e.g. figure 5.10, BA 8 activation). This warrants discussion as it could be expected that if a pure state effect was to be observed then it might be expected to be the HR+ would activate significantly differently to the controls. It has been proposed that certain brain regions show a 'capacity constraint' which is reflected in an initial increase in task-dependent activation which then reaches a plateau before falling away as task demands increase further (281,282). Although discussing specifically the parametric paradigm of Whalley et al., (139), Fletcher (281), with the aid of a diagram of inverted U responses to task difficulty, proposed that the genetic risk of schizophrenia is associated with a leftwards shift in this profile such that lower demands produce higher activation initially. This activation then falls away sooner than in the controls when demands increase. The HR+ could have decreased activation in some brain regions, particularly the PFC, sooner than both the HR- and the controls. As proposed earlier, the HR- are still able to compensate for their compromised ToM circuit more effectively than the HR+, who have lost this

compensatory ability by virtue of having had psychotic positive symptomatology, and consequently activate less than the HR-. Although they appear to be activating similarly to the controls the HR+ are falling away in their activation whilst the controls are actually increasing.

5.5.9 ToM vs. Con group differences

In the second condition, ToM vs. Jumbled images, the HRill group activated significantly greater in BA8. It could be that the HRill who as well as originally being at enhanced risk of the disease and then have the psychotic illness have a damaged mentalising circuit, particularly in the frontal lobes and the greater activation in BA8 could be an attempt to compensate for this compromised function in other regions.

The frontal eye field is located in BA8 and it is well documented that there are eye tracking abnormalities in individuals with schizophrenia associated with a pathophysiologic abnormality in this region (283). This increased activation could therefore arise from increased saccadic eye movements resulting from increased scanning of the image components in order to derive the correct meaning of the jokes in this group of individuals with schizophrenia.

In this contrast of analysis 1, significant group activation differences were observed in motor and supplementary motor regions than the controls. These motor areas have been previously shown to activate in the observation of human actions (as discussed in (259,284) and there were a lot of these depicted in the cartoon drawings used as stimuli, perhaps these activations could be as a result of the human mirror neuron system (although it should be noted that the drawings of human actions were implied

and of a 'frozen snapshot' by their very nature of being a single frame drawing). These group activation differences in these motor regions (BA4&6) could be from the HR groups finding it more difficult to get the jokes and hence looking at the jokes more so there will be more activation from observing the actions of the characters contained within the drawings.

There is also the possibility that some HR individuals were perhaps pushing the button differently (e.g. multiple presses, using several fingers and pushing very forcibly) such that after subtraction there were still remnants of the motor cortex activations via button pressing.

5.5.10 Medication

It is documented that atypical neuroleptics can normalize reduced frontoparietal activation as well as some neuropsychological test results (285-287). The medication effects on the HRill may be to alleviate prefrontal hypofrontality. Indeed, could the medication effects on the HRill group could be compensating for any impairment in the mentalising circuitry caused by psychotic sympotmatology, particularly in the frontal cortex? This appears to be unlikely as they scored significantly worse than the HR+Now on the ToM2 debrief score. However, caution is required interpreting the HRill group results due to the power issue (n=5). The MIP's for this group show both smaller and less activation clusters than those of the other groups.

5.5.11 Humour appreciation

Mentalising abilities and humour appreciation are both aspects of social cognition and there could therefore be a possible overlap with some brain regions being activated by both of these cognitive domains, hence these activations could represent a combination of both these social cognition faculties. Wild et al., (226) report that the right frontal cortex and left and right middle and inferior temporal regions are involved in the perception of humour. Comprehension of humour is thought to arise in the left temporal-occipital junction and temporal pole. These two regions may participate in the detection of incongruity. As mentioned previously there was only one significant within group activation in the temporal poles and this may reflect that this type of pictorial mentalising task does not require the use of social scripts.

The PFC is believed to correlate with humour integration because it manages responses to multiple stimuli while balancing the input of information. The DLPFC is involved in executive functioning and this may be crucial to examining, deconstructing and understanding humorous stimuli (266). The unique activation observed in BA11 in the Phy vs. Con contrast could be such a PFC humour elicited activation.

Goel & Dolan (288) showed that joke comprehension elicits increased right hemispheric activity whilst difficulty comprehending jokes has been associated with right hemisphere damage (289).

Although we can be sure that the observed ToM activations results are in agreement with the mentalising literature, some of the activations could be as a consequence of the humorous nature of the stimuli.

5.6 Conclusions

These results indicate that there is a state effect evident in ToM processing in those at high risk of schizophrenia, as observed differences were between the different HR groups but not the controls. The HRill and HR+ groups activating more frontal regions also support a state effect; the difference in activation being due to the experience of symptoms at, or at least relatively close to, the time of testing. This is consistent with a body of the neuropsychological ToM literature indicating impaired mentalising ability during psychotic episodes and fluctuating ability with symptom severity. The precise pattern of results we obtained is however complex and suggestive of state-trait interactions. The majority of group activation differences were observed in the PFC, providing further evidence for this region being a key component of schizophrenia risk.

6 General discussion and conclusions

6.1 Introduction

This chapter is a general discussion of the major findings of this thesis. Furthermore, limitations of the current findings will be discussed along with suggestions for future research.

This study was an investigation into mentalising abilities in individuals at enhanced risk of schizophrenia. Abilities were tested via neuropsychological assessment on a battery of two theory of mind tasks, the Hinting task and cartoon picture sequences, and a self-monitoring drawing task. The underlying neurobiology of mentalising was investigated with fMRI and a visual joke paradigm. The fMRI aspect of the study represented the first time that such individuals have had their mentalising abilities investigated by this method.

The aim of this study was to investigate whether there are compromised mentalising abilities in individuals at enhanced risk of schizophrenia and if so, were the observed group differences of a state or trait nature. Evidence for a trait effect, that observed mentalising deficits were due to being at enhanced risk, would include significant differences between the HR groups and the controls. Evidence for a state effect, would involve significant group differences between the HR+ and both the HR- and control groups, implying that current and past symptomatology cause the observed impairment in mentalising,. In order to test these two competing schemas, there were two analyses. Analysis 1 investigated both state and trait effects by comparing the HR+, HR- and control group to each other. Analysis 2 investigated solely state effect by splitting the HR+ into present and past symptomatic groups, HR+Now and HR+Ever respectively, and comparing them to each other and to a schizophrenia group, HRill. The HRill group was comprised of individuals who had begun their

participation in the EHRS as well individuals and had, over the course of their participation in the study, gone on to develop psychosis.

6.2 Neuropsychological investigation

As regards the neuropsychological tasks, we hypothesized that in analysis 1, the ever symptomatic relatives (HR+) would show ToM deficits compared to the controls and relatives who had never experienced psychotic symptoms (HR-). In analysis 2, it was hypothesized that those relatives who were known to have psychotic symptoms at the time of testing (recently symptomatic) would perform worse than currently asymptomatic relatives who had experienced psychotic symptoms in the past.

There were no observable significant between group differences in either analysis on the Hinting task. This task involves the attribution of intent to characters involved in 10 short scenarios and it appears that the sensitivity of this task coupled with the relatively small group numbers was such that group differences could not be identified.

The Brüne cartoons represented a more sensitive test in that rather than one particular mentalising question being asked each time (i.e. attribution of intent) a variety of questions pertaining to the mental states of the depicted cartoon characters were asked. These questions were of differing levels of mental state comprehension (e.g. first versus second order ToM) and consequent levels of difficulty. This task found no significant between group differences for the overall global task total. However, when each of the three cartoon subtotals and the 7 seven different question types were considered, then significant group differences were observed in analysis 1.

These supported the hypothesis for analysis 1 in that the HR+ individuals were found to perform significantly worse than both the controls and HR- participants.

The self-monitoring task provided evidence supporting the hypothesis for analysis 2, in that significant between group differences were observed between the HR+ groups with past and present symptoms with the HR+Now performing significantly worse than the HR+Ever on both the control and combined score total.

The findings from this neuropsychological study therefore provide evidence for compromised self-monitoring and ToM abilities in HR+ individuals of a state nature.

6.3 fMRI investigation

The fMRI visual joke task enabled us to investigate the neural correlates of mentalising processes within the groups. It was hypothesised that different activation patterns would be observed in the HR+ groups relative to the controls in three a priori chosen regions, the STS, PFC and temporal poles, based on the ToM imaging literature. This visual joke paradigm elicited robust activations across the groups in two of the hypothesised regions (the temporal poles appeared not to be greatly activated in this study) and in other regions associated with mentalising such as the precuneus and inferior parietal lobule. All but one of the between group differences were between the HR groups, and the majority of these were in the PFC, in the medial, middle and dorso-lateral aspects. In the main ToM vs. Phy contrast in analysis 1, the HR- activation was significantly greater than the HR+ in right BA7 and bilaterally in BA6. In the same contrast in analysis 2, the HR+Ever activation was greater than the HR+Now in the right BA8, and greater than the HRill also in right BA8. The HR+Now activation was significantly greater than the HR+Ever in

right BA9/46. In a third post hoc analysis combining the groups from analyses 1 and 2, the HR- activation was greater than the HR+Now bilaterally in BA8.

In the discussion of the previous chapter it was proposed that the observed PFC activation differences could be due to the HR individuals having an impaired ToM circuit as a direct consequence of their enhanced risk for schizophrenia. This status presumably therefore requires a compensatory mechanism which is evident in the increased PFC activations observed within these individuals.

The major finding of this thesis was that the HR individuals who had experienced psychotic symptoms were the most impaired on the neuropsychological tasks and activated significantly differently on the fMRI task (predominately in the PFC) relative to those HR individuals who had not reported experiencing such symptoms. Of those individuals who had such symptoms, it was those who had experienced them recently who were the most different from other groups. It is hypothesised that the putative compensatory mechanism fails in association with the development of these symptoms, with a larger failure evident in those individuals who are currently or have recently experienced such symptoms than those who have experienced such symptoms on a previous occasion.

The neuroimaging allowed the between group differences observed in the neuropsychological investigations to be further elaborated. This therefore appears to be a more sensitive means of investigation, which allowed the specific group brain activation patterns to be observed. The neuropsychological investigations differentiate participants via a score for correct or incorrect responses. The sensitivity of the imaging enables the difference in brain region activations to be observed. The major imaging finding was to show that although participants were able to give

correct interpretations of the jokes, as evidenced in the debrief session scores, there were significantly different between group brain activations, particularly in the PFC, to derive the answers.

6.4 Strengths and Limitations of current study

There were two major strengths to this study. As mentioned previously, the fMRI study is currently unique in that it represents the first time that relatives of individuals with schizophrenia have been imaged whilst performing a ToM task.

The second major strength of this study was that it was a combined neuropsychological and fMRI investigation. The neuropsychological aspect incorporated tasks requiring the appreciation of other people's mental states of both a verbal and pictorial nature. Furthermore, the inclusion of a self-monitoring task allowed the self perspective of the participants to also be investigated.

The major limitation of this study concerns the issue of statistical power, particularly in the second analysis. Indeed, critics would argue that these group numbers (6 vs. 6 vs. 5) are so small as to make it very difficult to draw any meaningful conclusions, particularly in relation to lack of significance, from the analyses. This power issue is more the case for the neuropsychological investigation than for the fMRI study.

However, we believe that the unusual and special nature of the participants compensates for this to a certain extent.

Some might be critical of both the state versus trait question and the splitting of the HR individuals on the basis of presence or absence of symptoms. State can be defined as some characteristic of the individual (a type of cognitive organisation or a facet of personality) that is present during episodes of the illness; whilst trait can be

defined as a more enduring characteristic that seems to precede the onset of complaints and which is often thought to be aetiologically important. Bentall (20) alleges that there are two problems with this distinction. Firstly, are these really two distinct types of psychological phenomenon? Psychological characteristics probably vary in their mutability from highly unstable and state-like to highly stable and trait-like. Secondly, it is often assumed that state-like processes are mere epiphenomena of symptoms and therefore causally unimportant. According to this way of thinking, unless the psychological characteristics that we observe in patients can be shown to be present prior to episodes, they can play no causal role.

In this study, the HR- and HR+ are considered as both having the same enhanced risk of schizophrenia. These two participant groups are separated from one another on the basis of the presence or absence of psychotic symptoms. An astute and anonymous reviewer of the neuropsychological data suggested that this may not be the case. It could be that the HR+ individuals are actually closer to the underlying psychosis-proneness, have a higher genetic loading and may have a stronger psychosis 'trait' in addition to the reported more psychotic-like experiences. In this way, the observed group differences on the ToM tasks could possibly be accounted for by the HR+ being closer to an underlying psychotic trait and not just as a result of the presence of psychotic symptoms.

As regards the fMRI analysis, the use of the physical cartoons as a 'control' task in comparison to the ToM cartoons may be considered by some to be a slight limitation in that there were activations observed in the physical jokes that were not observed in the ToM jokes.

Finally, I was not blind to the clinical status of the participants and as a consequence of this there is the possibility for biases of recording/measuring, performance and interpretation.

6.5 Improvements to this study

Having conducted this described investigation, there are several areas in which I believe improvements and extensions could be made if this study were to be conducted again. The first improvement would involve increasing the participant number and consequent group size, hence giving more statistical power, particularly to the neuropsychological aspect of the study.

The second improvement or modification relates to the choice of implemented fMRI task. Due to the incorporation of a DTI paradigm, discussed below, there was only time for one functional task within the scanning session of 1 hour. The visual joke task of Gallagher et al., (2000) that was implemented in this study included both humour and mentalising, and could therefore be said not to represent a pure ToM task in the strictest sense. As a result we cannot be fully certain that the PFC activation is due to mentalising processing or a combination of both humour and mentalising processing. In this way, a non humorous visual task could have been used instead, such as those pictorial sequences of Brunet et al., (117,195), Langdon et al., (105,113) and Sarfati et al., (102). This would have allowed ToM region activation to be observed without any humour appreciation involvement. If there had been no DTI paradigm and consequently more fMRI scan time, both the visual joke task and a non humorous visual task could have been run together and by subtracting the activations for the latter from the former, then alleged 'pure' humour activations could also have been studied.

Time allowing, a verbal story task could also have been implemented. It appears from the imaging literature that regardless of the modality of mentalising task utilised, the same core ToM regions are activated. However, combining both verbal

and pictorial paradigms with this clinical population would have been very interesting, as there may have been visual versus verbal group differences.

With different grouping of both stimuli and participants, there is a possibility of being able to conduct parametric analysis. For example, in the pilot study, participants could have been asked to state whether they found a joke easy, difficult or intermediate to comprehend and then these three levels of difficulty could be used to differentiate the physical and ToM cartoons in a subsequent parametric fMRI analysis. This would allow neural correlates to be investigated with increasing task difficulty, but would probably require more stimuli and participants.

The participant groups could have been further divided via the presence of symptomatology. The HR+Ever participants could have been separated on account of how many times have they reported symptoms in the past. For example, those who had only once reported such symptoms could be separated from those who had either reported them on more than one occasion or reported them on every clinical interview. Likewise, the HR+Now group could be split into groups based on those who are reporting symptoms for the first time versus those have reported such symptoms in the past also. These groups' performance on the neuropsychological tasks and their respective group fMRI data could then be compared and contrasted. This would, however, require much larger groups; probably no less than the entire EHRS cohort, to ensure that splitting these HR groups down into these subgroups would be viable.

6.6 The future:

6.6.1 Future work to be implemented on this data

It is intended to run a functional connectivity analysis on the imaging data set. Functional connectivity refers to observed correlations over time between different brain areas. For example, brain regions A and B may be considered to be functionally connected if an increase (or decrease) of activity in brain region A is associated-in time- with an increase (or decrease) in brain region B. The analysis of functional connections in fMRI is based on examining the correlation activity between regions by detecting inter-regional temporal correlations of the BOLD signal (81). This analysis will enable us to see what brain regions are related to each other in the appreciation of both the Physical and ToM cartoons.

The PFC and temporal lobes are connected to one another via two large white matter tracts. The uncinate fasiculus forms a connection between the orbital gyrus and parts of the middle and inferior frontal gyri with the anterior region of temporal lobe. The arcuate fasiculus connects the superior and middle frontal gyri with parts of the temporal lobe.

The integrity of these can be investigated via the technique of Diffusion Tensor Imaging (DTI). This is a technique that enables the diffusion of water in brain tissue to be visualised and measured. The technique is very good in studying white matter tracts in the brain as the mobility of water is restricted perpendicular to the axons orientated along the fibre tracts. This is a consequence of the concentric structure of multiple tightly packed myelin membranes wrapped around the axon tracts (290). Previous DTI studies investigating schizophrenia have shown decreased fractional

anisotropy in white matter due to loss of orientation and organisation of fibre tracts both in whole white matter and in particular tracts such as the corpus callosum and the uncinate fasiculus (e.g. (291)). We will use Voxel Based Morphometry (VBM) to normalise fractional anisotrophy (FA) maps to a High Risk FA template. The analysis of the FA maps will enable us to investigate the integrity of these fasiculae within each group. If the HR groups are found to have compromised fasiculae relative to the control group, then this could be evidence for the developmental model of schizophrenia and evidence for a trait effect of ToM abilities in those at enhanced risk of the disease. Structurally impaired fasiculae could result in both functional impairment and the impairment in connectivity between the frontal and temporal lobes. This could be the reason for compromised mentalising abilities in the HR+ individuals in this study and individuals with schizophrenia generally.

6.6.2 ToM tasks in Future High Risk investigations

This study occurred at the tail end of the EHRS, after almost a decade of study. The EHRS was a serial investigation into individuals at enhanced risk of schizophrenia due to the presence of the disease in first or second degree family members. All participants who took part in this mentalising investigation had been examined on several previous occasions, via MRI imaging, neuropsychological investigation and clinical interview. This allowed changes over time in any of these investigative areas to be observed in these individuals. In this particular investigation into mentalising abilities in a cohort of the EHRS, ToM ability was investigated in these individuals for the first and only time. Consequently, the neuropsychological task scores and fMRI neural activations are a "one off" and cannot therefore be compared to similar

data obtained on prior assessments of mentalising abilities. In future High Risk studies like the EHRS, a battery of both verbal and pictorial ToM tasks could be incorporated at the onset, such that changes over time in individuals mentalising abilities could be observed in those who go on to develop schizophrenia and HR individuals who experience transient psychotic symptoms. More longitudinal studies are required in both schizophrenia and High Risk groups in order to further investigate the state question of whether ToM abilities fluctuate with symptoms and symptom severity.

6.6.3 Future ToM neuroimaging research

There is a need for more ToM imaging studies in schizophrenia as there are currently very few. Those that there are, including this one, have single figure patient groups. Studies with much larger group numbers are required and such group numbers would allow patient groups to be further split on the basis of symptoms and diagnosis as has been done in some other areas of schizophrenia research. With so few current studies, we still do not know what the nature of the underlying neural network of compromised mentalising ability in the schizophrenic brain may be.

Functional imaging has revealed a mentalising circuit comprised of core brain regions that are consistently activated in ToM tasks, regardless of the modality used. However, it is not clear to what extent the observed activations, particularly as regards the PFC, are due to executive function and language processing as well as to mentalising abilities. It still remains to be revealed to what extent reasoning about different mental states depends upon shared versus unique functional and neural

systems. fMRI may well be able to further clarify whether ToM abilities are of a domain-specific or domain-general nature.

Future work could focus harder on streamlining the ToM circuit, by attempting to limit and separate out executive function and language from mentalising tasks. Some question however whether it will be possible to further reduce the ToM circuit (36).

Aside from investigating these diffuse neural circuits, fMRI investigations will also allow the refinement of the anatomical regions of the circumscribed ToM circuit, such that smaller more specific regions can be linked to particular mentalising task aspects (e.g.(207), have shown that a specific region of the TPJ, named TPJ-M by the authors, was specific to reasoning about the contents of mental states). This will rely on small volume corrections and region of interest fMRI paradigms rather than whole brain volume investigations such as the one implemented in this thesis.

As mentioned in a previous chapter, a criticism of both neuropsychological and imaging studies is that although they use paradigms that are easily experimentally manipulated and are thereby effective in an experimental environment, they do not necessarily reflect accurate or valid representations of real life in real time. Kim et al., (260) state that in real-life situations more valuable social information is conveyed through nonverbal emotional channels and not necessarily through overt verbal or non-emotional channels. This statement ties in with the proposal that ToM may have arisen through the monitoring of biological motion and others actions (219,220). In this way perhaps photographs and short video scenarios could be utilised in fMRI paradigms as an attempt to make the concerned tasks more applicable to what we see, hear and react to in everyday social interactions. Short

video scenarios will be information rich in social stimuli which will include: gestures, other body language information, facial content, eye gaze, as well as speech. With scan time being a relatively expensive commodity, researchers want to get value for money and acquire as much data as possible. The use of video scenarios will provide answers to both these requirements, being information rich and thus having the capacity to produce various activations. I envisage a greater use of such paradigms in the future, although their complexity may initially provide difficulties for interpretation.

6.7 Conclusions

This study represents the first time that individuals at enhanced risk of schizophrenia have been investigated on a combined neuropsychological and fMRI ToM paradigm. Evidence for a state, more than a trait effect was observed, with the significant group differences on both the neuropsychological task scores and fMRI activations primarily due to the experience of symptoms at, or at least relatively close to, the time of testing. Indeed, this state effect can be viewed as a graded (severity) effect, with HR participants with the most recent psychotic symptoms being the most impaired on the tasks and different in their fMRI activations relative to those HR individuals who had never experienced such symptomatology. Until this study is replicated in other high risk individuals, ideally with greater participant numbers, a degree of caution is warranted in the definitive interpretation of these results. It is however probably safe to say that this study demonstrates ToM impairments, and a putative neurobiological basis for them, that differs in subjects at different levels of high risk status for schizophrenia.

References

1. Brodmann K. Vergleichende Localisation de Grosshirnrinde. Leipzig: Barth; 1925.
2. Wilson BA, Alderman N, Burgess P, Emslie H, Evans JJ. Behavioural Assessment of the Dysexecutive Syndrome (BADS). Bury, St Edmunds: Thames Valley Test; 1996.
3. Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, Shaner A. A Manual for for the Expanded Brief Psychiatric Rating Scale. Int J Methods Psychiatr Res 1993;3:199-228.
4. Binois R, Pichot P. Test de Vocabulaire. Edition du Centre de Psychologie Appliquee, Paris 1947.
5. Lehrle S. Der MWT-ein Intelligenztest fur die arztliche. PraxisNeurolPsychiat 1976;&:488-491.
6. Nelson H, Willison J. The National Adult Reading Test manual. NFER-Wilson, editor: Windsor; 1991.
7. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa, IA: University of Iowa; 1984.
8. Andreasen NC. The Scale for the Assessement of Positive Symptoms (SAPS). Iowa City, IA: The University of Iowa; 1984.
9. Andreasen NC. Thought, language and communication disorders. Arch Gen Psychiatry 1979;36:1315-1330.
10. Morice R, Delahunty A. Frontal/executive impairments in schizophrenia. Schizophr Bull 1996;22(1):125-137.
11. Weschler D. Weschler Adult Intelligence Scale-Revised. London: Psychological Corporation; 1955/1982.
12. Weschler D. Weschler Adult Memory Scale-Revised. New York: Psychological Corporation; 1987.
13. Adolphs R. Social cognition and the human brain. Trends Cogn Sci 1999;3(12):469-479.
14. Brothers L. The social brain: a project for integrating primate behaviour and neurophysiology in a new domain. Concepts in Neuroscience 1990;1:27-51.
15. Russell T, Sharma T. Social Cognition at the Neuaral Level:Investigations in Autism,Psychopathy and Schizophrenia. In: Brune M, Ribbery H, Schiefenhovel W, editors. The Social Brain:Evolution and Pathology: John Wiley & Sons; 2003. p 253-276.
16. Dunbar R. The social brain hypothesis. Evol Anthropol 1998;6:178-190.
17. Abu-Akel A. A neurobiological mapping of theory of mind. Brain Res Brain Res Rev 2003;43(1):29-40.
18. Premack D, Woodruff G. Does the chimpanzee have a theory of mind? Behavioural and Brain Sciences 1978;4:515-526.
19. Frith C, Frith U. The physiological basis of theory of mind:functional neuroimaging studies. In: Baron-Cohen S, Tager-Flisberg H, Cohen D, editors. Understanding other Minds:Perspectives from developmental

cognitive neuroscience. second edition ed. Oxford: Oxford University Press; 2000.

20. Bentall RP. Madness Explained psychosis and human nature. London: Penguin; 2003.
21. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind"? Cognition 1985;21(1):37-46.
22. Burns JK. An evolutionary theory of schizophrenia: cortical connectivity, metarepresentation, and the social brain. Behav Brain Sci 2004;27(6):831-855; discussion 855-885.
23. Brüne M. "Theory of Mind" in Schizophrenia: A Review of the Literature. Schizophrenia Bulletin 2005;31(1):21-42.
24. Brüne M, Brüne-Cohrs U. Theory of mind--evolution, ontogeny, brain mechanisms and psychopathology. Neuroscience & Biobehavioral Reviews;In Press, Corrected Proof.
25. Malle BF. The relation between language and theory of mind in development and evolution. In: Givon T, Malle BF, editors. The evolution of language out of pre-language. Amsterdam: Benjamins; 2002. p 265-284.
26. Frith U, Frith CD. Development and neurophysiology of mentalizing. Philos Trans R Soc Lond B Biol Sci 2003;358(1431):459-473.
27. Abu-Akel A, Abushus'leh A. 'Theory of Mind' in violent and nonviolent patients with paranoid schizophrenia. Schizophrenia Research 2004;69:45-53.
28. Dunbar RIM. Theory of Mind and the evolution of language. In: Harford JR, Kennedy MS, Knight C, editors. Approaches to the Evolution of Language:Social and cognitive bases. Cambridge: Cambridge University Press; 1998. p 92-110.
29. Garfield JL, Peterson CC, Perry T. Social Cognition, Language Acquistion and The Development of the Theory of Mind. Mind & Language 2001;16(5):494-541.
30. Baron-Cohen S. The evolution of theory of mind. In: Corballis MC, Lea SEG, editors. The Descent of Mind:Psychological Perspectives on Hominid Evolution. New York: Oxford University Press; 1999.
31. Sperber D, Wilson D. Pragmatics, Modularity and Mind-reading. Mind & Language 2002;17:3-23.
32. Greig TC, Bryson GJ, Bell MD. Theory of mind performance in schizophrenia: diagnostic, symptom, and neuropsychological correlates. J Nerv Ment Dis 2004;192(1):12-18.
33. Corcoran R, Frith CD. Autobiographical memory and theroy of mind:evidence of a relationship in schizophrenia. Psychological Medicine 2003;33:897-905.
34. Corcoran R, Frith CD. Thematic reasoning and theory of mind.Accounting for social inference difficulties in schizophrenia. Evolutionary Psychology 2005;3:1-19.
35. Brüne M, Bodenstein L. Proverb comprehension reconsidered-'theory of mind' and the pragmatic use of language in schizophrenia. Schizophr Res 2005;75(2-3):233-239.
36. Apperly IA, Samson D, Humphreys GW. Domain-specificity and theory of mind: evaluating neuropsychological evidence. Trends in Cognitive Sciences 2005;9(12):572-577.

37. Gallup G. Self-awareness and the emergence of mind in primates. American Journal of Psychiatry 1982;2:237-248.
38. Gallup G. Self-awareness and the evolution of social intelligence. Behavioral Processes 1998;42:239-247.
39. Fenigstein A, Scheier MF, Buss AH. Public and private self-consciousness:Assessment and theory. Journal of Consulting and Clinical Psychology 1975;43:522-527.
40. Johnson AK, Barnacz A, Yokkaichi T, Rubio J, Racioppi C, Shackelford TK, Fisher ML, Keenan JP. Me, myself, and lie: The role of self-awareness in deception. Personality and Individual Differences 2005;38(8):1847-1853.
41. Baron-Cohen S. The essential difference. New York: Basic Books; 2003.
42. Fodor J. The Modularity of Mind. MA: MIT Press; 1983.
43. Leslie AM. Pretense and representation: The origins of "Theory of Mind". Psychological Review 1987;94(4):412-426.
44. Scholl BJ, Leslie AM. Modularity, development and 'theory of mind.' Mind and Language 1999;14:131-153.
45. Leslie AM, Friedman O, German TP. Core mechanisms in "theory of mind". Trends Cogn Sci 2004;8(12):528-533.
46. Samuels R. Evolutionary Psychology and the Massive Modularity Hypothesis. Br J Philos Sci 1998;49(4):575-602.
47. Chomsky N. Knowldege of Language:Its Nature, Origin and use. New York: Preager; 1986.
48. Vogeley K, Bussfield P, Newen A, Herrmann S, Happe F, Falkai P, Maier W, Shah NJ, Fink GR, K Z. Mind reading: Neural mechanisms of theory of mind and self-perspective. NeuroImage 2001;14:170-181.
49. Vollm BA, Taylor ANW, Richardson P, Corcoran R, Stirling J, McKie S, Deakin JFW, Elliott R. Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. NeuroImage 2006;29(1):90-98.
50. Stone VE, Gerrans P. Does the normal brain have a theory of mind? Trends in Cognitive Sciences 2006;10(1):3-4.
51. Harris PL. From simulation to folk psychology:the case for development. Mind and Language 1992;7:120-144.
52. Volkmar FR, Pauls D. Autism. The Lancet 2003;362:1133-1141.
53. Frith CD. The Cognitive Neuropsychology of Schizophrenia. Hove: Lawrence Earlbaum Associates; 1992.
54. Frith U, Morton J, Leslie AM. The cognitive basis of a biological disorder:autism. Trends in the Neurosciences 1991;14(433-438).
55. Frith U, Happe F, Siddons F. Autism and Theory of Mind in everyday life. Social Development 1994;3:108-123.
56. Kraepelin E. Psychiatrie, ein lehrbuch fur studierende und arzte. Leipzig: Barth; 1896.
57. Bleuler E. Dementia praecox oder gruppe der schizophrenien. [Dementia praecox or the group of schizophrenias]. Press IU, translator. New York; 1911.
58. Schneider K. Clinical psychopathology. Stratton HMGa, translator. New York; 1959.

59. Wong AHC, Van Tol HHM. Schizophrenia: from phenomenology to neurobiology. Neuroscience & Biobehavioral Reviews 2003;27(3):269-306.
60. Fuller RLM, Schultz SK, Andreasen NC. The symptoms of schizophrenia. In: Hirsch SR, Weinberger DR, editors. Schizophrenia. Massachusetts, USA: Blackwell; 2003.
61. Leiberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, Gilmore J. The early stages of schizophrenia:Speculations on pathogenesis, pathophysiology and the therapeutic approaches. Biological Psychiatry 2001;50:884-897.
62. Hafner H, Hambrecht M, Loffler W, Munk-Jorgensen P, Riecher-Rossler A. Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. Psychol Med 1998;28(2):351-365.
63. Mueser KT, McGurk SR. Schizophrenia. Lancet 2004;363(9426):2063-2072.
64. American Psychiatric Association. Diagnostic and Statistical Manual for mental disorders. Washington DC; 1994.
65. Organisation WH. Schedules for clinical assessment in neuropsychiatry. Geneva: World Health Organisation; 1993.
66. Brüne M. Schizophrenia-an evolutionary enigma? Neurosciance and Biobehavioral Reviews 2004;28:41-53.
67. Gottesman I. Schizophrenia genisis: the origins of madness. In: Attkinson RC, Lindzey G, Thompson RF, editors. New York: WH Freeman & Co; 1991.
68. Done DJ, Crow TJ, Johnstone EC, Sacker A. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. BMJ 1994;309:699-703.
69. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994;344(8934):1398-1402.
70. Honey G, Bullmore E. Human pharmacological MRI. Trends in Pharmacological Sciences 2004;25(7):366-374.
71. Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 1998;172:110-120.
72. Abu-Akel A. The neurochemical hypothesis of 'theory of mind'. Med Hypotheses 2003;60(3):382-386.
73. Garety PA, Freeman D. Cognitive approaches to delusions: a critical review of theories and evidence. Br J Clin Psychol 1999;38 (Pt 2):113-154.
74. Bentall RP, Kinderman P, Kaney S. The self, attributional processes and abnormal beliefs: Towards a model of persecutory delusions. Behaviour Research and Therapy 1994;32:331-341.
75. Charlton B. Theory of miind delusions and bizarre delusions in an evolutionary perspective:psychiatry and the social brain. In: Brune M RHSW, editor. The Social Brain-Evolution and Pathology. Chichester: John Wiley & Sons; 2003.
76. Johns LC, Nazroo JY, Bebbington P, Kuipers E. Occurrence of hallucinatory experiences in a community sample and ethnic variations. Br J Psychiatry 2002;180:174-178.

77. Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. Schizophrenia Research 2002;54(1-2):59-65.
78. Johnstone EC, Abukmeil SS, Byrne M, Clafferty R, Grant E, Hodges A, Lawrie SM, Owens DGC. Edinburgh high risk study-findings after four years:demographic, attainment and psychpathological issues. Schizophrenia Research 2000(46):1-15.
79. Poulton R, Caspi A, Moffit TE, Cannon M, Murray RM, Harrington H. Children's Self-Reported Psychotic Symptoms and Adult Schizophreniform Disorder. Archives of General Psychiatry 2000;57(11):1053-1058.
80. Lawrie S. The neuropsychology of schizophrenia. In: Johnstone EC, Humphreys M, Lang F, Lawrie S, Sandler R, editors. Schizophrenia Concepts and Clinical Management. Cambridge UK: Cambridge University Press; 1999. p 129-144.
81. Whyte MC. Neuropsychological Assessment and Functional Magnetic Resonance Imaging of Verbal Declarative Memory performance in Relatives of Schizophrenia Patients and Controls. PhD Thesis, University of Edinburgh; 2005.
82. Wimmer H, Perner J. Beliefs about beliefs: Representations and constraining function of wrong beliefs in young children's understanding of deception. Cognition 1983;13:103-128.
83. Baron-Cohen S, Leslie A, Frith U. Mechanical, behavioural and intentional understanding of picture stories in autistic children. British Journal of Developmental Psychology 1986;4:113-125.
84. Leslie AM, Thaiss L. Domain specificity in conceptual development: neuropsychological evidence from autism. Cognition 1992;43(3):225-251.
85. Leslie A, Roth D. What can autism teach us about metarepresentation? In: Baron-Cohen et al., editor. Understanding other Minds: Perspective from Autism. Oxford: Oxford University Press; 1993.
86. Frith CD. Theory of mind in Schizophrenia. In: David AS, Cutting JC, editors. The Neuropsychology of Schizophrenia. Hove: Laurence Erlbaum Associates; 1994.
87. Gallagher S. Neurocognitive models of schizophrenia: A neurophenomenological model. 2004.
88. Frith C. Comments on Shaun Gallagher: neurocognitive models of schizophrenia: a neurophenomenological critique. Psychopathology 2004;37(1):20-22.
89. Frith C. Schizophrenia and theory of mind. Pschological Medicine 2004;34:385-389.
90. Abu-Akel A, Bailey AL. Correspondence : Letter to the editor. Pschological Medicine 2000;30:735-738.
91. Hardy-Baylé MC. Organisatin de l'action, phénomées de consciance et représentation mentale de l'action chez des schizophrénes. Actualitiés Psychiatriques 1994;20:393-400.
92. Andreasen NC. Scale for the assessment of thought, language and communication (TLC). Schizophr Bulletin 1986;12(3):473-482.
93. Hardy-Baylé MC, Sarfati Y, Passerieux C. The cognitive basis of disorganization symptomatology in schizophrenia and its clinical correlates:

toward a pathogenetic approach to disorganization. Schizophr Bull 2003;29(3):459-471.

94. Wimmer H, Perner J. Beliefs about beliefs: representation and constraining function of wrong beliefs in young childrens understanding of deception. Cognition 1983;13:103-128.
95. Perner J, Wimmer H. 'John thinks that Mary thinks that...' Attribution of socond-order beliefs by 5 to 10-year-old children. J Exp Child Psychology 1985;39:437-471.
96. Siegal M, Varley R. Neural systems involved in "theory of mind". Nat Rev Neurosci 2002;3(6):463-471.
97. Friedman O, Leslie AM. A developmental shift in processes underlying successful belief-desire reasoning. Cognitive Science 2004;28(6):963-977.
98. Corcoran R, Mercer G, Frith C. Schizophrenia, symptomatology and social inference:Investigating "theory of mind" in people with schizophrenia. Schizophrenia Research 1995;17:5-13.
99. Frith CD, Corcoran R. Exploring 'theory of mind' in peoiple with schizophrenia. Pschological Medicine 1996;26:521-530.
100. Corcoran R, Cahill C, Frith CD. The appreciation of visual jokes in people with schizophrenia: a study of 'mentalising' ability. Schizophrenia Research 1997(24):319-327.
101. Sarfati Y, Hardy-Baylé MC, Nadel J, Chevalier JF, Widlöcher D. Attribution of mental states to others in schizophrenic patients. Cognitive Neuropsychiatry 1997;2:1-17.
102. Sarfati Y, Hardy-Baylé MC, Besche C, Widlöcher D. Attribution of intentions to others in people with schizophrenia:a non verbal exploration with comic strips. Schizophrenia Research 1997(25):199-209.
103. Sarfati Y, Hardy-Baylé MC, Brunet E, Widlöcher D. Investigating theory of mind in schizophrenia:influence of verbalisation in disorganized and non-disorganised patients. Schizophrenia Research 1999(37):183-190.
104. Sarfati Y, Passerieux C, Hardy-Baylé MC. Can verbalization remedy the Theory of MInd deficit in Schizophrenia. Psychopathology 2000;33:246-251.
105. Langdon R, Mitchie PT, Ward PB, McConaghy N, Catts SV, Coltheart M. Defective Self and/or Other Mentalising in Schizophrenia: A Cognitive Neuropsychological Approach. Cognitive Neuropsychiatry 1997;2(3):167-193.
106. Doody GA, Gotz M, Johnstone EC, Frith CD, Cunningham-Owens DG. Theory of Mind and psychoses. Pschological Medicine 1998;28:397-405.
107. Drury VM, Robinson EJ, Birchwood M. 'Theory of mInd' skills during an acute episode of psychosis and following recovery. Pschological Medicine 1998;28:1101-1112.
108. Mitchley NJ, Barber J, Gray JM, Brooks DN, Livingston MG. Comprehension if irony in Schizophrenia. Cognitive Neuropsychiatry 1998;3(2):127-138.
109. Sarfati Y, Hardy-Baylé MC. How do people with schizophrenia explain the behaviour of others? A study of theory of mind and its relationship to thought and speech disorganization in schizophrenia. Psychol Med 1999;29(3):613-620.

110. Sullivan RJ, Allen JS. Social deficits associated with schizophrenia defined in terms of interpersonal Machiavellianism. Acta Psychiatr Scand 1999;99(2):148-154.
111. Mazza M, De Risio A, Surian L, Roncone R, Casacchia M. Selective impairments of theory of mind in people with schizophrenia. Schizophrenia Research 2001;47:299-308.
112. Pickup G, Frith CD. Theory of mind impairments in schizophrenia:symptomatology, severity and specificity. Pschological Medicine 2001;31:207-220.
113. Langdon R, Coltheart M, Ward PB, Catts SV. Mentalising, executive planning and disengagement in schizophrenia. Cognitive Neuropsychiatry 2001;6(2):81-108.
114. Herold R, Tenyi T, Lenard K, Trixler M. Theory of mind deficit in people with schizophrenia during remission. Pschological Medicine 2002;32:1125-1129.
115. Langdon R, Coltheart M, Ward PB, Catts SV. Disturbed communication in schizophrenia: the role of poor pragmetaics and poor mind reading. Pschological Medicine 2002;32:1273-1284.
116. Roncone R, Falloon IR, Mazza M, De Risio A, Pollice R, Necozione S, Morosini P, Casacchia M. Is theory of mind in schizophrenia more strongly associated with clinical and social functioning than with neurocognitive deficits? Psychopathology 2002;35(5):280-288.
117. Brunet E, Sarfati Y, Hardy-Bayle MC, Decety J. Abnormalities of brain function during a nonverbal theory of mind task in schizophrenia. Neuropsychologia 2003;41(12):1574-1582.
118. Brüne M. Theory of mind and the role of IQ in chronic disorganised schizophrenia. Schizophrenia Research 2003;60:57-64.
119. Janssen I, Krabbendam L, Jolles J, van Os J. Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. Acta Psychiatrica Scandinavica 2003;180:110-117.
120. Mazza M, De Risio A, Tozzini C, Roncone R, Casacchia M. Machiavellianism and Theory of Mind in people affected by schizophrenia. Brain Cogn 2003;51(3):262-269.
121. Gambini O, Barieri V, Scarone S. Theory of mInd in schizophrenia: First person vs third person perspective. Consciousness and Cognition 2004;13:39-46.
122. McCabe R, Leuder I, Antaki C. Do people with schizophrenia display theory of mind deficits in clinical interactions. Pschological Medicine 2004;34:401-412.
123. Schiffman J, Lam CW, Jiwatram T, Ekstrom M, Sorensen H, Mednick S. Perspective-taking deficits in people with schizophrenia spectrum disorders: a prospective investigation. Psychol Med 2004;34(8):1581-1586.
124. Brüne M. Emotion recognition, 'theory of mind', and social behaviour in schizophrenia. Psychiatry Research 2005;133(2-3):135-147.
125. Marjoram D, Tansley H, Miller P, MacIntyre D, Owens DG, Johnstone EC, Lawrie S. A theory of mind investigation into the appreciation of visual jokes in schizophrenia. BMC Psychiatry 2005;5(1):12.

126. Schenkel LS, Spaulding WD, Silverstein SM. Poor premorbid social functioning and theory of mind deficit in schizophrenia: evidence of reduced context processing? J Psychiatr Res 2005;39(5):499-508.
127. Zalla T, Bouchilloux N, Labruyere N, Georgieff N, Bougerol T, Franck N. Impairment in event sequencing in disorganised and non-disorganised patients with schizophrenia. Brain Research Bulletin 2006;68:195-202.
128. Langdon R, Coltheart M. Mentalising, schizotypy, and schizophrenia. Cognition 1999;71:43-71.
129. Corcoran R. Theory of Mind in other clinical populations. Is a selective theroy of mind deficit exclusive to autism? In: Baron-Cohen S, Tager-Flisberg H, Cohen JD, editors. Understanding other mindsPerspectives from Developmental Cognitive Neuroscience. Oxford: Oxford University Press; 2000. p 391-421.
130. Corcoran R. Theory of mind and schizophrenia. In: DL CPP, editor. Social Cognition and Schizophrenia. Washington DC: American Psychological Association; 2001. p 149-174.
131. Corcoran R. Inductive reasoning and the understanding of intention in schizophrenia. Cognitive Neuropsychiatry 2003;8:223-235.
132. Kerr N, Dunbar RIM, Bentall RP. Theory of Mind deficits in bipolar affective disorder. Journal of Affective Disorders 2003;73:253-259.
133. Marjoram D, Gardner C, Burns J, Miller P, Lawrie S, Johnstone E. Symptomatology and social inference: A theory of mind study of schizophrenia and psychotic affective disorder. Cognitive Neuropsychiatry 2005;10 (5):347-359.
134. Inoue Y, Tonooka Y, Yamada K, Kanba S. Deficiency of theory of mind in patients with remitted mood disorder. J Affect Disord 2004;82(3):403-409.
135. Hodges A, Byrne M, Grant E, Johnstone E. People at risk of schizophrenia. Sample characteristics of the first 100 cases in the Edinburgh High-Risk Study. Br J Psychiatry 1999;174:547-553.
136. Johnstone EC, Ebmeier KP, Miller P, Owens DG, Lawrie SM. Predicting schizophrenia: findings from the Edinburgh High-Risk Study. Br J Psychiatry 2005;186:18-25.
137. Wing JK, Cooper JE, Sartorius N. Measurement and classification of psychiatric symptoms: an instruction manual for the PSE and CATEGO program. New York: Cambridge University Press; 1974.
138. Johnstone E, Cosway R, Lawrie S. Disinguishing characteristics of subjects with good and poor early outcome in the Edinburgh High-Risk Study. British Journal of Psychiatry 2002;181(43):s26-s29.
139. Whalley HC, Simonotto E, Marshall I, Ebmeier KP, Owens DGC, Goddard NH, Johnstone EC, Lawrie SM. fMRI correlates of state and trait effects in subjects at genetically enhanced risk of schizophrenia. Brain 2004(127):478-490.
140. Whalley HC. Functional neuroimaging in subjects at high genetic risk of schizophrenia. PhD Thesis,University of Edinburgh; 2005.
141. Byrne M, Hodges A, Grant E, Owens DC, Johnstone EC. Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS). Psychological Medicine 1999;29(29):1161-1173.

142. Byrne M, Clafferty BA, Cosway R, Grant E, Hodges A, Whalley HC, Lawrie SM, Owens DG, Johnstone EC. Neuropsychology, genetic liability, and psychotic symptoms in those at high risk of schizophrenia. J Abnorm Psychol 2003;112(1):38-48.
143. Lawrie SM, Whalley HC, Kestelman JN, Abukmeil SS, Byrne M, Hodges A, Rimmington JE, Best JJK, Owens DGC, Johnstone EC. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. The Lancet 1999(353):30-33.
144. Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, Best JJ, Owens DG, Johnstone EC. Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. Biol Psychiatry 2001;49(10):811-823.
145. Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Voxel-based morphometry of grey matter densities in subjects at high risk of schizophrenia. Schizophr Res 2003;64(1):1-13.
146. McIntosh A, Baig B, J,, Hall J, Job D, Whalley HC, Lymer GKS, Moorhead TWJ, Owens DG, Miller P, Porteous D, Lawrie S, M,, Johnstone EC. Realtionship of COMT varaints to brain strucutre and function in a population of high risk of psychosis. Biological Psychiatry 2006;Submitted.
147. Wyatt RJ, Henter I. Rationale for the study of early intervention. Schizophrenia Research 2001;51(1):69-76.
148. Kelemen O, Keri S, Must A, Benedek G, Janka Z. No evidence for impaired 'theory of mind' in unaffected first-degree relatives of schizophrenia patients. Acta Psychiatr Scand 2004;110(2):146-149.
149. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry 2001;42(2):241-251.
150. Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res 2004;71(2-3):285-295.
151. Johnson MK, Hashtroudi S, Lindsay DS. Source monitoring. Psychol Bull 1993;114(1):3-28.
152. Henquet C, Krabbendam L, Dautzenberg J, Jolles J, Merckelbach H. Confusing thoughts and speech: source monitoring and psychosis. Psychiatry Res 2005;133(1):57-63.
153. Jeannerod M. The mechanism of self-recognition in humans. Behav Brain Res 2003;142(1-2):1-15.
154. Kircher TT, Leube DT. Self-consciousness, self-agency, and schizophrenia. Conscious Cogn 2003;12(4):656-669.
155. Blakemore SJ, Frith CD. Self-awareness and action. Current opinion in neurobiology 2003;13(2):219-224.
156. Frith CD, Blakemore SJ, Wolpert DM. Abnormalities in the awareness and control of action. Philos Trans R Soc Lond B Biol Sci 2000;355(1404):1771-1788.
157. Feinberg I. Efference copy and corollary discharge: implications for thinking and its disorders. Schizophr Bull 1978;4(4):636-640.

158. Malenka RC, Angel RW, Hampton B, Berger PA. Impaired central error-correcting behavior in schizophrenia. Arch Gen Psychiatry 1982;39(1):101-107.
159. Frith C. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. Pschological Medicine 1987(17):631-648.
160. Frith CD, Done DJ. Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. Psychol Med 1989;19(2):359-363.
161. Mlakar J, Jensterle J, Frith CD. Central monitoring deficiency and schizophrenic symptoms. Pschological Medicine 1994(24):557-564.
162. Daprati E, Franck N, Georgieff N, Proust J, Pacherie E, Dalery J, Jeannerod M. Looking for the agent: an investigation into consciousness of action and self-consciousness in schizophrenic patients. Cognition 1997;65(1):71-86.
163. Stirling JD, Hellewell JSE, Quraishi N. Self-Monitoring dysfunction and the schizophrenic symptoms of alien control. Pschological Medicine 1998(28):675-683.
164. Blakemore SJ, Smith J, Steel R, Johnstone CE, Frith CD. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychol Med 2000;30(5):1131-1139.
165. Knoblich G, Stottmeister F, Kircher T. Self-monitoring in patients with schizophrenia. Psychol Med 2004;34(8):1561-1569.
166. Krabbendam L, Vermissen D, Janssen I, Franck N, Georgieff N, van Os J. Action monitoring in psychosis:Evidence for alterations in patients, non-psychotic reltaives, and subjects with psychotic experiences. Conference Abstract. Schizophrenia Bulletin:XX International Congress on Schizophrenia Research 2005;31(2):364.
167. World Health Organisation. Schedules for clinical assessment in neuropsychiatry. Geneva: World Health Organisation; 1993.
168. Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RS, Dolan RJ. Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature 1994;368(6472):633-635.
169. Whyte MC, McIntosh A, Johnstone EC, Lawrie SM. Declarative memory in unaffected adult relatives of patients with schizophrenia: A systematic review and meta-analysis. Schizophr Res 2005;78(1):13-26.
170. Stirling JD, Hellewell JSE, Ndlovu D. Self-Monitoring dysfunction and the positive symptoms of schizophrenia. Psychopathology 2001;34:198-202.
171. Turken AU, Vuilleumier P, Mathalon DH, Swick D, Ford JM. Are impairments of action monitoring and executive control true dissociative dysfunctions in patients with schizophrenia? Am J Psychiatry 2003;160(10):1881-1883.
172. Matthews PM. An introduction to functional magnetic resonance imaging of the brain. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI: An introduction to methods. Oxford UK: Oxford University Press; 2001. p 3-34.
173. Niznikiewicz MA, Spencer KM, Salisbury DF, McCarley RW. Event related potentials. In: Lawrie S, Johnstone EC, Weinberger DR, editors.

Schizophrenia:From Neuroimaging to Neuroscience. Oxford UK: Oxford University Press; 2004. p 293-329.

174. Rosburg T, Sauer H. Magnetoencephalography. In: Lawrie S, Johnstone E.C, Weinberger DR, editors. Schizophrenia:From Neuroimaging to Neuroscience. Oxford UK: Oxford University Press; 2004. p 331-347.
175. Heinz A, Romero B, D.R. W. Functional mapping with a single-photon emission computed tomography and positron emission tomography. In: Lawrie S, Johnstone EC, Weinberger DR, editors. Schizophrenia:From Neuroimaging to Neuroscience. Oxford UK: Oxford University Press; 2004. p 167-211.
176. Ogawa S, Lee TM, Kay A, R,, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 1990;87:9868-9872.
177. Jezzard P, Clare S. Principles of nuclear magnetic resonance and MRI. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI: An introduction to methods. Oxford UK: Oxford University Press; 2001. p 67-92.
178. Tofts PS. The Measurement Process: MR Data collection and Image Analysis. In: Tofts PS, editor. Quantative MRI of the Brain:Measuring changes caused by disease. Chichester UK: John Wiley & Sons; 2003. p 17-54.
179. Gjedde A. Brain energy metabolism and the physiological basis of the haemodynamic response. In: Jezzard P, Matthews PM, Smith SM, editors. Functional fMRI: An introduction to methods. Oxford UK: Oxofrd University Press; 2001. p 37-66.
180. Hoge RD, Pike GD. Quantative measurement using fMRI. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI:An introduction to Methods. Oxford UK: Oxford University Press; 2001. p 159-174.
181. Jezzard P, Ramsey NF. Functional MRI. In: Tofts PS, editor. Quantative MRI of the Brain:Measuring changes caused by disease. Chichester UK: John Wiley & Sons; 2003. p 413-454.
182. Donaldson DI, Buckner RL. Effective paradigm design. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI: An introduction to Methods. Oxford UK: Oxford University Press; 2001. p 177-195.
183. Aguirre GK, D'Esposito M. Experimental design for brain fMRI. In: Moonen CTW, Bandettini PA, editors. Functional MRI: Springer; 1998.
184. Culham J. Functional Neuroimaging: Experimental Design and Analysis. In: Cabeza R, Kingstone A, editors. Handbook of Functional Neuroimaging of Cognition (2nd Edition): MIT press; 2006.
185. Donaldson DI. Parsing brain activity with fMRI and mixed designs:what kind of a state is neuroimaging in? Trends in Neuroscience 2004;27:442-444.
186. Brammer MJ. Head motion and its correction. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI:An introduction to Methods. Oxford UK: Oxford University Press; 2001. p 243-250.
187. Ashburner J, Good CD. Spatial Registration of Images. In: Tofts PS, editor. Quantative MRI of the Brain: Measuring changes caused by disease. Chichester UK: John Wiley & Sons; 2003. p 503-531.

188. Saxe R, Carey S, N. K. Understanding other Minds: Linking developmental psychology and Functional Neuroimaging. Annual Review of Psychology 2004;55:87-124.
189. Jarrold C, Butler DW, Cottington EM, Jimenez F. Linking theory of mind and central coherence bias in autism and in the general population. Dev Psychol 2000;36(1):126-138.
190. Baron-Cohen S, Ring H, Moriarty J, Schmitz B, Costa D, Ell P. Recognition of mental state terms. Clinical findings in children with autism and a functional neuroimaging study of normal adults. Br J Psychiatry 1994;165(5):640-649.
191. Fletcher PC, Happe F, Frith U, Baker SC, Dolan RJ, Frackowiak RSJ, Frith CD. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition 1995;57:109-128.
192. Goel V, Grafman J, Sadato N, Hallett M. Modeling other minds. Neuroreport 1995;6(13):1741-1746.
193. Happé F, Ehlers S, Fletcher PC, Frith U, Johansson M, Gillberg C, Dolan R, Frackowiak RSJ, Frith CD. 'Theory of MInd' in the brain. Evidence from a PET scan study of Asperger syndrome. Neuroreport 1996;20(8):197-201.
194. Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, Williams SCR. Social intelligence in the normal and autistic brain: an fMRI study. European Journal of Neuroscience 1999;11(6):1891-1898.
195. Brunet E, Sarfati Y, Hardy-Bayle MC, Decety J. A PET investigation of the attribution of intentions with a nonverbal task. Neuroimage 2000;11(2):157-166.
196. Castelli F, Happe F, Frith U, Frith CD. Movement and Mind: A functional imaging study of perception and interpretation of complex intentional movement patterns. NeuroImage 2000;12:314-325.
197. Gallagher HL, Happe F, Brunswick N, Fletcher PC, Frith U, Frith CD. Reading the mind in cartoons and stories: an fMRI study of theory of mind in verbal and nonverbal tasks. Neuropsychologia 2000;38(1):11-21.
198. Russell TA, Rubia K, Bullmore ET, Soni W, Suckling J, Brammer MJ, Simmons A, Williams SCR, Sharma T. Exploring the social brain in schizophrenia: Left prefrontal underactivation during mental state attribution. American Journal of Psychiatry 2000(157):2040-2042.
199. Sabbagh MA, Taylor M. Neural correlates of theory-of-mind reasoning: an event-related potential study. Psychol Sci 2000;11(1):46-50.
200. McCabe K, Houser D, Ryan L, Smith V, Trouard T. A functional imaging study of cooperation in two-person reciprocal exchange. Proc Natl Acad Sci U S A 2001;98(20):11832-11835.
201. Berthoz S, Armony JL, Blair RJ, Dolan RJ. An fMRI study of intentional and unintentional (embarrassing) violations of social norms. Brain 2002;125(Pt 8):1696-1708.
202. Calder AJ, Lawrence AD, Keane J, Scott SK, Owen AM, Christoffels I, Young AW. Reading the mind from eye gaze. Neuropsychologia 2002;40(8):1129-1138.

203. Castelli F, Frith C, Happe F, Frith U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain 2002;125(8):1839-1849.
204. Blakemore S-J, Boyer P, Pachot-Clouard M, Meltzoff A, Segebarth C, Decety J. The Detection of Contingency and Animacy from Simple Animations in the Human Brain. Cereb Cortex 2003;13(8):837-844.
205. Calarge C, Andreasen NC, O'leary DS. Visualising how one brain understands another:A PET study of ToM. American Journal of Psychiatry 2003;160:1954-1964.
206. Kampe KK, Frith CD, Frith U. "Hey John": signals conveying communicative intention toward the self activate brain regions associated with "mentalizing," regardless of modality. J Neurosci 2003;23(12):5258-5263.
207. Saxe R, Kanwisher N. People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind". Neuroimage 2003;19(4):1835-1842.
208. Wicker B, Perrett DI, Baron-Cohen S, Decety J. Being the target of another's emotion: a PET study. Neuropsychologia 2003;41(2):139-146.
209. Decety J, Jackson PL, Sommerville JA, Chaminade T, Meltzoff AN. The neural bases of cooperation and competition: an fMRI investigation. Neuroimage 2004;23(2):744-751.
210. Gallagher HL, Frith CD. Dissociable neural pathways for the perception and recognition of expressive and instrumental gestures. Neuropsychologia 2004;42(13):1725-1736.
211. German TP, Niehaus JL, Roarty MP, Giesbrecht B, Miller MB. Neural correlates of detecting pretense: automatic engagement of the intentional stance under covert conditions. J Cogn Neurosci 2004;16(10):1805-1817.
212. Ishii R, Gojmerac C, Stuss DT, Gallup GG, Jr., Alexander MP, Chau W, Pantev C. MEG analysis of "theory of mind" in emotional vignettes comprehension. Neurol Clin Neurophysiol 2004;30:2004-2028.
213. Liu D, Sabbagh MA, Gehring WJ, Wellman HM. Decoupling beliefs from reality in the brain: an ERP study of theory of mind. Neuroreport 2004;15(6):991-995.
214. Rilling JK, Sanfey AG, Aronson JA, Nystrom LE, Cohen JD. The neural correlates of theory of mind within interpersonal interactions. Neuroimage 2004;22(4):1694-1703.
215. Walter H, Adenzato M, Ciaramidaro A, Enrici I, Pia L, Bara BG. Understanding intentions in social interaction: the role of the anterior paracingulate cortex. J Cogn Neurosci 2004;16(10):1854-1863.
216. den Ouden HE, Frith U, Frith C, Blakemore SJ. Thinking about intentions. Neuroimage 2005.
217. Hynes CA, Baird AA, Grafton ST. Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. Neuropsychologia 2005.
218. Kim J-W, Kim J-J, Jeong BS, Ki SW, Im D-M, Lee SJ, Lee HS. Neural mechanism for judging the appropriateness of facial affect. Cognitive Brain Research 2005;25(3):659-667.
219. Frith CD, Frith U. Interacting minds-A biological Basis. SCIENCE 1999;286:1692-1695.

220. Frith U, Frith CD. The biological basis of social interaction. Current Directions in Psychological Science 2001;10:151-155.
221. Gallagher HL, Frith CD. Functional imaging of 'theory of mind'. Trends Cogn Sci 2003;7(2):77-83.
222. Baron-Cohen S, Jollife T, Mortimer C, Robertson MM. Another advanced test of theory of mind :evidence from very high functioning adults with autism or asperger syndrome. J Child Psychol Psychiatry 1997;38(7):813-822.
223. Foot H. The psychology of humour and laughter. In: Cochrane RaC, E., editor. Psychology and Social Issues:A Tutorial text. London: Taylor and Francis; 1991. p 1-13.
224. Delay J, Pichot P, Guibert M, and Perse J. Un test d'appreciation de l'humour. Application dans la paranoia. RevPsycholAppl 1954;4:297-315.
225. Kant I. Kant's critique of judgement. J.H.Bernard, translator. New York: Hafner; 1972.
226. Wild B, Rodden FA, Grodd W, Ruch W. Neural correlates of laughter and humour. Brain 2003;126(Pt 10):2121-2138.
227. Shammi P, Stuss DT. The effects of normal aging on humor appreciation. J Int Neuropsychol Soc 2003;9(6):855-863.
228. Brown WS, Paul LK, Symington M, Dietrich R. Comprehension of humor in primary agenesis of the corpus callosum. Neuropsychologia 2005;43(6):906-916.
229. Ammons RB, Ammons CH. The Quick Test. Missoula: MT: Psychological Test Specialists; 1962.
230. Krawiecka M, Glodberg D, Vaughan MA. A standardised psychiatric assessment scale for rating chronic psychotic patients. Acta Psychiatrica Scandinavica 1977;55:299-308.
231. Atkins M, Burgess A, Bottomly C, Riccio M. Chlorpromazine equivalents: A consensus of opinion for both clinical and research implication. Psychiatric Bulletin 1997;21:224-226.
232. Woods S. Chlorpromazine equivalent doses for newer atypical antipsychotics. Journal of Clinical Psychiatry 2003;64:663-666.
233. Harrow M, O'connell EM, Herbenser ES, Altman ES, Kaplan KJ, Jobe TH. Disordered verbalizations in schizophrenia: a speech disturbance or thought disorder. Comprehensive Psychiatry 2003;44(5):353-359.
234. Hardy-Baylé MC, Sarfati Y, Olivier V, Besche C, Lefrere F, Passerieux C. Conscience intentionelle et schizophrenie. L'Encephale 1996;3:104-107.
235. Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Miller P, Best JJK, Owens DGC, Johnstone EC. Temporal lobe volume changes in people at high risk of schizophrenia with psychotic symptoms. British Journal of Psychiatry 2002;181:138-143.
236. Shenton M, Chandlee CD, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophrenia Research 2001(49):1-52.
237. Whalley HC, Whyte MC, Johnstone EC, Lawrie SM. Neural correlates of enhanced genetic risk for schizophrenia. Neuroscientist 2005;11(3):238-249.
238. Marjoram D, Miller P, McIntosh AM, Cunningham Owens DG, Johnstone EC, Lawrie SM. A neuropsychological investigation into 'Theory of Mind' and enhanced risk of schizophrenia. Psychiatry Research 2006;In Press.

239. Keshavan MS, Diwadkar VA, Spencer SM, Harenski KA, Luna B, Sweeney JA. A preliminary functional magnetic resonance imaging study in offspring of schizophrenic parents. Prog Neuropsychopharmacol Biol Psychiatry 2002;26(6):1143-1149.
240. Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinksi B, Weinberger DR. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. Am J Psychiatry 2003;160(4):709-719.
241. Thermenos HW, Seidman LJ, Breiter H, Goldstein JM, Goodman JM, Poldrack R, Faraone SV, Tsuang MT. Functional magnetic resonance imaging during auditory verbal working memory in nonpsychotic relatives of persons with schizophrenia: a pilot study. Biol Psychiatry 2004;55(5):490-500.
242. Blackwood DH, Glabus M, Dunan J, O'Carroll RE, Muir WJ, Ebmeier KP. Altered cerebral perfusion measured by SPECT in relatives of patients with schizophrenia. Correlations with memory and P300. Br J Psychiatry 1999;175:357-366.
243. O'Driscoll GA, Florencio PS, Gagnon D, Wolff A-LV, Benkelfat C, Mikula L, Lal S, Evans AC. Amygdala-hippocampal volume and verbal memory in first-degree relatives of schizophrenic patients. Psychiatry Research: Neuroimaging 2001;107(2):75-85.
244. Olevitch BA, Stern JA. Head movements in schizophrenia: new biological marker, critical neurological flaw, or artifact of subvocalization? Int J Neurosci 1996;88(3-4):249-260.
245. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. 3 dimensional proportional syatem: an approach too cerebral imaging. Inc. New York: Thieme Medical Publishers,; 1988.
246. Platek SM, Keenan JP, Gallup GG, Feroze M. Where am I? The neurological correlates of self and the other. Cognitive Brain Research 2004;19(2):114-122.
247. Frederikse M, Lu A, Aylward E, Barta P, Sharma T, Pearlson G. Sex differences in inferior parietal lobule volume in schizophrenia. Am J Psychiatry 2000;157(3):422-427.
248. Andreasen NC, Nopoulos P, O’Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biological Psychiatry 1999;46(7):908-920.
249. Ho BC, Mola C, Andreasen NC. Cerebellar dysfunction in neuroleptic naive schizophrenia patients: clinical, cognitive, and neuroanatomic correlates of cerebellar neurologic signs. Biol Psychiatry 2004;55(12):1146-1153.
250. Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR. Pathological laughter and crying: a link to the cerebellum. Brain 2001;124(Pt 9):1708-1719.
251. Stone VR, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. Journal of Cognitive Neuroscience 1998;10(5):640-656.
252. Shallice T. 'Theory of Mind' and the prefrontal cortex. Brain 2001;124(2):247-248.

253. Ferstl EC, von Cramon DY. What Does the Frontomedian Cortex Contribute to Language Processing: Coherence or Theory of Mind? NeuroImage 2002;17(3):1599-1612.
254. Happé F, Brownell H, Winner E. Acquired 'theory of mind' impairments following stroke. Cognition 1999;70(3):211-240.
255. Rowe AD, Bullock PR, Polkey CE, Morris RG. "Theory of mind" impairments and their relationship to executive functioning following frontal lobe excisions. Brain 2001;124(Pt 3):600-616.
256. Stuss DT, Gallup GR, Alexander MP. The frontal lobes a re necessary for 'theory of mind'. Brain 2001;124:279-286.
257. Shamay-Tsoory SG, Tomer R, Berger BD, Goldsher D, Aharon-Peretz J. Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. Cogn Behav Neurol 2005;18(1):55-67.
258. Bird CM, Castelli F, Malik O, Frith U, Husain M. The impact of extensive medial frontal lobe damage on 'Theory of Mind' and cognition. Brain 2004;127(Pt 4):914-928.
259. Blakemore S-J, Frith C. The role of motor contagion in the prediction of action. Neuropsychologia 2005;43(2):260-267.
260. Kim J, Doop ML, Blake R, Park S. Impaired visual recognition of biological motion in schizophrenia. Schizophr Res 2005.
261. Bentaleb LA, Beauregard M, Liddle PF, Stip E. Cerebral activity associated with auditory verbal hallucinations: a functional magnetic resonance imaging case study. Journal of Psychiatry and Neuroscience 2002;28(3):217-218.
262. McGuire PK, Silbersweig DA, Frith CD. Functional neuroanatomy of verbal self-monitoring. Brain 1996;119 (Pt 3):907-917.
263. Shergill SS, Brammer MJ, Fukuda R, Williams SC, Murray RM, McGuire PK. Engagement of brain areas implicated in processing inner speech in people with auditory hallucinations. Br J Psychiatry 2003;182:525-531.
264. Schultz J, Imamizu H, Kawato M, Frith CD. Activation of the human superior temporal gyrus during observation of goal attribution by intentional objects. J Cogn Neurosci 2004;16(10):1695-1705.
265. Saxe R, Wexler A. Making sense of another mind: The role of the right temporo-parietal junction. Neuropsychologia 2005;43(10):1391-1399.
266. Azim E, Mobbs D, Jo B, Menon V, Reiss AL. Sex differences in brain activation elicited by humor. PNAS 2005;102(45):16496-16501.
267. Kawashima R, Sugiura M, Kato T, Nakamura A, Hatano K, Ito K, Fukuda H, Kojima S, Nakamura K. The human amygdala plays an important role in gaze monitoring: A PET study. Brain 1999;122(4):779-783.
268. Holzman PS. Eye movement dysfunctions and psychosis. Int Rev Neurobiol 1985;27:179-205.
269. Weinberger DR, Berman KF. Prefrontal function in schizophrenia:confounds and controversies. In: Roberts AC, Robbins TW, Weiskrantz L, editors. The Prefrontal Cortex: Executive and Cognitive Functions. Oxford: Oxford University Press; 1998.
270. Manoach DS. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr Res 2003;60(2-3):285-298.

271. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci 2003;3(4):255-274.
272. Volz KG, Schubotz RI, Cramon DY. Variants of uncertainty in decision-making and their neural correlates. Brain Res Bull 2005;67(5):403-412.
273. Fiddick L, Spampinato MV, Grafman J. Social contracts and precautions activate different neurological systems: An fMRI investigation of deontic reasoning. Neuroimage 2005.
274. Petrides M. Monitoring of selections of visual stimuli and the primate functional cortex. Proceedings Biological Sciences 1991;246(1317):293-298.
275. Bach LJ, Happe F, Fleminger S, Powell J. Theory of Mind:Independence of executive function and the role of the frontal cortex in acquired brain injury. Cognitive Neuropsychiatry 2000;5((3)):175-192.
276. Ranganath C, Johnson MK, D'Esposito M. Prefrontal activity associated with working memory and episodic long-term memory. Neuropsychologia 2003;41(3):378-389.
277. Habeck C, Rakitin BC, Moeller J, Scarmeas N, Zarahn E, Brown T, Stern Y. An event-related fMRI study of the neural networks underlying the encoding, maintenance, and retrieval phase in a delayed-match-to-sample task. Brain Res Cogn Brain Res 2005;23(2-3):207-220.
278. Zysset S, Huber O, Ferstl E, von Cramon DY. The anterior frontomedian cortex and evaluative judgment: an fMRI study. Neuroimage 2002;15(4):983-991.
279. Robbins TW. Dissociating executive functions of the prefrontal cortex. In: Roberts AC, Robbins TW, Weiskrantz L, editors. The Prefrontal Cortex: Executive and Cognitive functions. Oxford: Oxford University Press; 1998.
280. Sabbagh MA. Understanding orbitofrontal contributions to theory-of-mind reasoning: implications for autism. Brain Cogn 2004;55(1):209-219.
281. Fletcher PC. Functional neuroimaging of schizophrenia: from a genetic predisposition to the emergence of symptoms. Brain 2004;127(3):457-459.
282. Callicott J, Weinberger DR. Neuropsychiatric dynamics: the study of mental illness using functional magnetic resonance imaging. European Journal of Radiology 1999(30):95-104.
283. Sweeney JA, Luna B, Srinivasagam NM, Keshavan MS, Schooler NR, Haas GL, Carl JR. Eye tracking abnormalities in schizophrenia: evidence for dysfunction in the frontal eye fields. Biol Psychiatry 1998;44(8):698-708.
284. de C. Hamilton AF, Wolpert DM, Frith U, Grafton ST. Where does your own action influence your perception of another person's action in the brain? Neuroimage 2005.
285. Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SC, Sharma T. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. Proc Natl Acad Sci U S A 1999;96(23):13432-13437.
286. Braus DF, Brassen S. Functional magnetic resonance imaging and antipsychotics. Overview and own data. Radiologe 2005;45(2):178-185.
287. Davis CE, Jeste DV, Eyler LT. Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. Schizophr Res 2005;78(1):45-60.

288. Goel V, Dolan RJ. The functional anatomy of humor: segregating cognitive and affective components. Nat Neurosci 2001;4(3):237-238.
289. Coulson S, Williams RF. Hemispheric asymmetries and joke comprehension. Neuropsychologia 2005;43(1):128-141.
290. Kubicki M, Westin CF, Nestor PG, Wible CG, Frumin M, Maier SE, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. Biol Psychiatry 2003;54(11):1171-1180.
291. Burns J, Job D, Bastin ME, Whalley H, Macgillivray T, Johnstone EC, Lawrie SM. Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. Br J Psychiatry 2003;182:439-443.
292. Happé FG, Winner E, Brownell H. The getting of wisdom: theory of mind in old age. Dev Psychol 1998;34(2):358-362.
293. Sullivan K, Tager-Flisberg H. Second-order belief attribution in Williams syndrome:intact or impaired? American Journal of Mental Retardation 1999;104(6):523-532.
294. Walston F, Blennerhassett RC, Charlton B. "Theory of Mind", persecutory delusions and the somatic marker mechanism. Cognitive Neuropsychiatry 2000;5((3)):161-174.
295. Cuerva AG, Sabe L, Kuzis G, Tiberti C, Dorrego F, Starkstein SE. Theory of mind and pragmatic abilities in dementia. Neuropsychiatry Neuropsychol Behav Neurol 2001;14(3):153-158.
296. Gregory C, Lough S, Stone V, Erzinclioglu S, Martin L, Baron-Cohen S, Hodges JR. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. Brain 2002;125(Pt 4):752-764.
297. Maylor EA, Moulson JM, Muncer AM, Taylor LA. Does performance on theory of mind tasks decline in old age? Br J Psychol 2002;93(Pt 4):465-485.
298. Richell RA, Mitchell DG, Newman C, Leonard A, Baron-Cohen S, Blair RJ. Theory of mind and psychopathy: can psychopathic individuals read the 'language of the eyes'? Neuropsychologia 2003;41(5):523-526.
299. Snowden JS, Gibbons ZC, Blackshaw A, Doubleday E, Thompson J, Craufurd D, Foster J, Happe F, Neary D. Social cognition in frontotemporal dementia and Huntington's disease. Neuropsychologia 2003;41(6):688-701.
300. Channon S, Sinclair E, Waller D, Healey L, Robertson MM. Social cognition in Tourette's syndrome: intact theory of mind and impaired inhibitory functioning. J Autism Dev Disord 2004;34(6):669-677.
301. Dolan M, Fullam R. Theory of mind and mentalizing ability in antisocial personality disorders with and without psychopathy. Psychol Med 2004;34(6):1093-1102.
302. McDonald S, Flanagan S. Social perception deficits after traumatic brain injury: interaction between emotion recognition, mentalizing ability, and social communication. Neuropsychology 2004;18(3):572-579.
303. Shaw P, Lawrence EJ, Radbourne C, Bramham J, Polkey CE, David AS. The impact of early and late damage to the human amygdala on 'theory of mind' reasoning. Brain 2004;127(Pt 7):1535-1548.
304. Bibby H, McDonald S. Theory of mind after traumatic brain injury. Neuropsychologia 2005;43(1):99-114.

305. Bora E, Vahip S, Gonul AS, Akdeniz F, Alkan M, Ogut M, Eryavuz A. Evidence for theory of mind deficits in euthymic patients with bipolar disorder. Acta Psychiatrica Scandinavica 2005;112(2):110-116.
306. Channon S, Pellijeff A, Rule A. Social cognition after head injury: sarcasm and theory of mind. Brain Lang 2005;93(2):123-134.
307. Dziobek I, Rogers K, Fleck S, Hassenstab J, Gold S, Wolf OT, Convit A. In search of "master mindreaders": Are psychics superior in reading the language of the eyes? Brain and Cognition 2005;58(2):240-244.
308. Farrant A, Morris RG, Russell T, Elwes R, Akanuma N, Alarcon G, Koutroumanidis M. Social cognition in frontal lobe epilepsy. Epilepsy & Behavior 2005;7(3):506-516.
309. Lee L, Harkness KL, Sabbagh MA, Jacobson JA. Mental state decoding abilities in clinical depression. J Affect Disord 2005;86(2-3):247-258.
310. Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. Neuropsychologia 2005;In Press, Corrected Proof.
311. Tchanturia K, Happe F, Godley J, Treasure J, Bara-Carril, Schmidt U. 'Theory of Mind' in anorexia nervosa. European Eating Disorders Review 2005;12(6):361-366.
312. Harvey PD. Reality monitoring in mania and schizophrenia. The association of thought disorder and performance. J Nerv Ment Dis 1985;173(2):67-73.
313. Bentall RP, Baker GA, Havers S. Reality monitoring and psychotic hallucinations. Br J Clin Psychol 1991;30 (Pt 3):213-222.
314. Brebion G, Amador X, David A, Malaspina D, Sharif Z, Gorman JM. Positive symptomatology and source-monitoring failure in schizophrenia -- an analysis of symptom-specific effects. Psychiatry Research 2000;95(2):119-131.
315. Fourneret P, Franck N, Slachevsky A, Jeannerod M. Self-monitoring in schizophrenia revisited. Neuroreport 2001;12(6):1203-1208.
316. Franck N, Farrer C, Georgieff N, Marie-Cardine M, Dalery J, d'Amato T, Jeannerod M. Defective recognition of one's own actions in patients with schizophrenia. Am J Psychiatry 2001;158(3):454-459.
317. Lindner A, Thier P, Kircher TT, Haarmeier T, Leube DT. Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. Curr Biol 2005;15(12):1119-1124.

Appendix

Table 1 : Mentalising studies in other non-schizophrenia and autism clinical populations

Study	*Population*	*ToM Tasks*	*Findings/Deficit*
(292) Happe *et al.*, (1998)	19 Elderly participants (Mean age 73 yrs, 10 females, 9 males) 52 healthy young participants (mean age 21 yrs, 25 men, 27 females).	Theory of Mind stories Physical stories Jumbled text.	Elderly group performed better than young adults on the theory of mind stories but not on control stories or jumbled passages. Authors suggest that it could be that although performance on tasks with non-mental content may decrease with age, performance on ToM tasks remains intact and may even improve in later adult years.
(254) Happe *et al.*, (1999)	Right Hemisphere Damage patients (n=14) Matched Controls (n=19).	ToM cartoon task.	RHD patients performed significantly worse than controls on the ToM task.
(293) Sullivan and Tager-Flushberg, (1999)	22 children with Williams syndrome (13 females, 8males) 14 children with Prader Willi syndrome (4 females, 10 males) 13 children with non-specific retardation (7 females, 6 males).	2 second-order belief stories (taken from the study of Sullivan).	All groups were impaired on second order false belief questions but approximately 2/3 of group participants could pass ignorance questions.
(294) Walston *et al.*, (2000)	4 males with pure cases of encapsulated persecutory delusions.	Corcoran and Frith (Corcoran et al., 1995, 1997; Frith and Corcoran, 1996) devised ToM tasks: Humorous cartoons (ToM set and Physical set) Written narratives Hinting Task.	All four participants with encapsulated persecutory delusions had intact ToM abilities. Authors conclude that in this instance, these deluded individuals do not have a faulty ToM mechanism, rather the delusions stem from the inferencing of the somatic marker mechanism.
(275) Bach *et al.*, (2000)	1 male with orbito-frontal (OF) damage	Neuropsychological battery Executive function tasks ToM stories and cartoons.	Ability of patient to understand mental states and affective responses was found to be intact and independent of executive functioning. Evidence is provided that ToM ability appears to be independent of executive

			skills of overall strategy formation and not necessarily dependent on OF involvement. Evidence further supports the modular hypothesis of ToM and that this ability may be supported by more posterior regions.
(295) Cuerva *et al., (2001)*	Alzheimers Patients (n=34) Age Matched Controls (n=10).	Second Order belief story 11 short social situation stories Pragmatic abilities tested via indirect requests and conversational implications.	65% failure of AD group on second order ToM story. Association between ToM task failure and pragmatic deficits.
(255) Rowe *et al.,* (2001)	31 unilateral frontal lobe lesion patients: right sided (n=15) left sided (n=16) Controls (n=31).	First and second false belief stories Battery of executive function tasks.	Both patient groups were significantly impaired on the ToM tasks. They also exhibited a range of deficits in executive functions but these were independent of the observed ToM impairments.
(256) Stuss *et al.,* (2001)	Frontal lobe lesion patients: Right Frontal (n=4) Left frontal (n=8) Bifrontal (n=7) Right nonfrontal (n=5) Left nonfrontal (n=8) Control (n=14).	Visual perspective taking task Deception task.	Lesions in frontal lobes, particularly on the right, significantly impaired ability on the perspective taking task. Medial frontal lesions, particularly right ventral, impaired detection of deception.
(296) Gregory *et al.,* (2002)	Frontal variant frontotemporal dementia (fvFTD) (n=19) Alzheimer's patients (n=12) Matched Controls (n=16).	First and second order ToM tasks Faux pas detection Eyes task.	fvFTD failed all ToM tasks while the Alzheimer's group only failed on the second order ToM. Faux pas test results showed fvFTD failed on ToM based questions whilst Alzheimer's group failed on memory based questions only.
(297) Maylor *et al.,* (2002)	Young Adults (mean age 21 yrs) Old Young Adults (mean age 67) Old old Adults (mean age 81).	ToM stories ToM stories with need to remember information Non mental state attribution control stories.	Young performed significantly better than both the older groups on ToM stories with a memory load. Young and Old young groups performed significantly better than the old old group on ToM stories without a memory load. No difference on the control stories.
(132) Kerr *et al.,* (2003)	Bipolar-manic (n=20) Bipolar-	6 ToM stories, resting first and second order beliefs and deception.	Impaired performance was observed in both bipolar-manic and bipolar depressed

	depressed (n=15) Bipolar-remission (n=13) Controls (n=15).		manic, controlling for memory. Remitted patients performed similarly to controls.
(298) Richell *et al.*, (2003)	Psychopathic inmate group (n=19) Matched non-psychopathic controls (n=18).	Reading the mind in the Eyes task.	Psychopathic individuals did not present with any observable compromised function compared to the controls.
(299) Snowden *et al.*, (2003)	Frontotemporal dementia group (n=13) Huntington's disease (n=13) Controls (n=18).	ToM stories ToM cartoons Eyes task.	FTD exhibited impairment on all tasks, regardless of whether task involved attribution of mental state. HD's showed a milder impairment in cartoon and story tasks and normal preference judgments.
(258) Bird *et al*., (2004)	1 individual with a bilateral anterior cerebral artery infarction.	2 Picture sequences, 1 ToM, 1 Non-ToM (Baron-Cohen et al., 1986) 16 short ToM passages (Happe et al., 1995) Violation of social norms task (Berthoz et al., 2002) Faux Pas test (Baron-Cohen at al., 1999) Attribution of intent to animations (Abell et al., 2002; Castelli et al., 2000, 2002).	Patient's performance on all tasks bar social norm task was well within the range of healthy subjects. Had problems judging embarrassing situations as being "embarrassing" on social norms task.
(300) Channon *et al.*, (2004)	Tourette Syndrome group (n=15) Matched Controls (n=23).	8 ToM stories 8 non mentalistic stories Interpersonal Reactivity Index (Empathy measuring).	No observable differences on the ToM tasks between the groups.
(301) Dolan & Fullam (2004)	Anti-Personality Disordered subjects (ASPDs n=89) Controls (n=20).	First and second order stories Faux pas Eyes Task.	No differences on stories. ASPD's could detect the faux pas but showed indifference on impact of these. ASPD's showed impairments on recognitions of basic emotions.
(134) Inoue *et al.*, (2004)	Unipolar or bipolar patients in remission (n=50) Matched healthy controls (n=50).	A four picture sequence cartoon scenario. Participants were asked to correctly sequence the pictures and answer 4 ToM question types: First-order false belief; second-order false belief, reality question and a tactical deception question.	Remitted mood disorder group showed significantly impaired performance on the second –order false belief question compared to the control group. There were no significant group differences on the other 3 question types. There was no correlation with the four question types and IQ (as measured by the WAIS-R).
(302) McDonald & Flanagan	Traumatic Brain Injury group (n=34)	Videotaped conversational exchanges. Questions based on these conversations of	Clinical group had difficulty judging most facets of social information, ability to

(2004)	Controls (n=34).	second order ToM, lying and sarcasm.	understand second order ToM judgments was related to ability to understand conversational inference.
(303) Shaw *et al.*, (2004)	Individuals with amygdala lesions: Early damage (n=15) Late damage (n=11) Non amygdale lesion group (n=14) Controls (n=38).	ToM stories Metaphor and irony task. Faux pas task. Conflicting belief and emotion task.	Early damage group significantly impaired to all other groups, particularly on more advanced ToM tasks (e.g irony). Late damage group not impaired relative to other groups.
(304) Bibby and McDonald (2004)	Traumatic brain injury (TBI n=15) Controls (n=15).	First and second order story tasks ToM cartoon task Non-mental state inference tasks.	The clinical group performed worse than the controls on both task types. This could not be accounted for by the working memory or implicit language demands of the tasks.
(305) Bora *et al.*, 2005	43 euthymic bipolar patients 30 healthy controls.	Eyes task Hinting Task Extensive neuropsychological battery.	Bipolar patient group was impaired on both ToM tasks and showed impairment on in many cognitive tasks, relative to the control group. Evidence of impaired mentalising abilities in bipolar patients. Authors suggest that executive function and other cognitive deficits may be partly responsible for this.
(306) Channon *et al.*, (2005)	Closed Head Injury Group (n=19) Controls (n=19).	Sarcasm Task Human action comprehension task.	CHI group poorer at comprehending sarcasm from sincere remarks and human action from physical events.
(307) Dziobek *et al.*, (2005)	22 Psychics 22 Controls.	"Reading the Mind in the Eyes" test Interpersonal Reactivity Index.	No group difference on the "Eyes" task. Physics were shown to have more cognitive empathy.
(308) Farrant *et al.*, (2005)	Frontal lobe epilepsy (FLE n=14) Controls (n=14).	ToM stories Faux pas Task Mental and physical cartoon humour appreciation.	FLE not impaired on story tests of ToM and only a trend for impairment on faux pas task. However, they were impaired on humour appreciation of both ToM and physical cartoon and on recognition of facial emotion and perception of eye gaze expression. Social cognition impairments were therefore evident with relative sparing of ToM.

(309) Lee et al., (2005)	Female unipolar depression group (n=52) Female healthy control group (n=30).	Eyes Task.	Depressed group significantly impaired to controls.
(310) Lough *et al.*, (2005)	Frontotemporal dementia group (n=18) Matched controls (n=13)	ToM cartoon task (Corcoran and Frith, 1997) ToM stories (Happe et al., 1996) Moral/conventional distinction task Social situations task.	fvFTD were significantly impaired on ToM cartoon task but not stories. Knowledge of social rules was intact, but moral reasoning was defective. ToM was independent of observed executive function deficits. Social reasoning is disrupted in a number of ways in fvFTD.
(133) Marjoram *et al.*, (2005)	Affectives (n=15) Schizophrenia individuals (n=15) Controls (n=15).	New version of the Hinting task.	Schizophrenia group performed significantly worse than affectives and control groups. Poor performance was found to be significantly linked to presence of delusions & hallucinations, regardless of diagnosis.
(257) Shamay-Tsoory *et al.*, (2005)	Prefrontal Cortex lesion group (n=26) Posterior lesion group (n=13) Controls (n=13).	Second order false belief task. Irony Task. Faux pas task.	PFC group significantly impaired on irony and faux pas tasks relative to other groups. Regions in right VM area associated with most severe ToM deficit.
(311) Tchanturia *et al.*, 2004	20 female patients with Anorexia Nervosa (AN) 20 female healthy controls.	ToM and control stories ToM cartoons and control cartoons.	Individuals with AN performed worse than HC subjects on ToM and control tasks. There was, however, no evidence of any selective impairment of ToM in AN sufferers. Authors conclude that these findings do not support a specific link between impaired ToM and AN.

Table 2 ***Self-Monitoring studies***

Study	*Population*	*Tasks*	*Finding*
(158) Malenka *et al.*, (1982)	14 schizophrenia 12 alcoholics 12 controls.	A step-function tracking task designed to prevent the use of exteroceptive signals in correcting errors of movement. A joystick control task in which subjects had to correct their errors very rapidly in the absence of visual feedback.	The schizophrenia group was significantly worse at correcting errors than the other groups. The results suggest that schizophrenics are deficient in the ability to monitor ongoing motor behavior on the basis of internal, self-generated cues.
(312) Harvey (1985)	20 schizophrenia 20 Manic patients *Both psychiatric groups were equally divided into groups of thought-disordered (TD) and non-thought-disordered (NTD)* 10 controls.	Task 1: Had to distinguish between words read out by two different experimenters. Task 2: Had to distinguish between words they had read out and words they had imagined.	TD patients were impaired on these tasks in the following ways: TD schizophrenics had problems differentiating information that they had said from information they had thought. TD manics had problems discriminating information presented by two external sources. Controls and NTD patients performed similarly.
(160) Frith & Done (1989)	23 acute psychotic patients 6 controls.	Modified version of Malenka et al., (1982) task such that task was presented to participants as a computer game.	Subgroup of schizophrenia group who had experiences of alien control of their thoughts and actions were significantly less likely to make error corrections in the absence of visual feedback. Authors suggest that these symptoms are a consequence of problems with the central monitoring of responses.
(313) Bentall *et al.*, (1991)	19 schizophrenics with hallucinations 15 psychotic individuals with delusions 22 controls	Source memory task. Participants had to generate category items (Think of a fruit beginning with P……) and had items read out to them (Plum). A week later participants were presented with a source-identification task, a list was read out to them containing the words the subject had supplied and the words previously read to the subject by the experimenter.	The psychiatric patients were less accurate in identifying the source of the items in comparison with the normal controls. Hallucinators were more likely to attribute to the reading lists items they had generated themselves. The authors interpreted the results as being consistent with the hypothesis that hallucinations are self-generated events misattributed to an external source.
(161) Mlakar *et al.*, (1994)	25 schizophrenic patients with Schneiderian symptoms.	Drawing task involving simple geometric shapes (Precursor of modified drawing task of Stirling et al.,	Compared to the control group and the two patient groups without Schneiderian symptoms, the schizophrenia

	14 schizophrenic patients without Schneiderian symptoms. 16 non-schizophrenic psychiatric paptients 10 healthy controls.	1998; 2001) which had to be drawn with both a joystick and keyboard keys with and without feedback.	group with Schneiderian symptoms had great difficulty in keeping track of their performance and remembering what actions they had made.
(162) Deprati *et al.*, (1997)	30 schizophrenia patients with and without and hallucinations and /or delusional experiences. 30 controls.	Execution of simple finger and wrist movements without direct visual control of their hand. Image of either their hand or an alien hand executing same or different movement was shown on a screen. Participants had to discriminate whether hand presented was theirs or not.	Hallucinating and deluded schizophrenic patients were more impaired on discriminating their own hand from the alien one and than the non –hallucinating ones. They also tended to misattribute the alien hand to themselves.
(163) Stirling *et al.*, (1998)	35 schizophrenia patients 24 controls.	2 self-monitoring tasks: Odd-even test: tested subjects' ability to correct errors. Drawing test: Left right test No feedback Feedback Battery of other neuropsychological and cognitive tests.	Schizophrenia group performed worse than the controls on the self-monitoring battery. Those who were experiencing symptoms of alien control tended to experience greater difficulty with each of the self-monitoring tests and this effect appeared to be independent of neuropsychological or general cognitive function.
(164) Blakemore *et al.*, (2000)	23 schizophrenics 18 individuals with affective disorder (n=18) These patient groups were then split into the following symptom groups via PANSS: 15 patients with auditory hallucinations and/or passivity experiences 23 patients with auditory hallucinations and/or passivity experiences 15 controls.	Assessment of response to tactile stimulation. Subjects were asked to rate the perception of a tactile sensation on the palm of their left hand. The tactile stimulation was either self-produced by the movement of the subject's right hand or externally produced by the experimenter.	Normal control subjects and those psychiatric patients with neither auditory hallucinations nor passivity phenomena experienced self-produced stimuli as less intense, tickly and pleasant than identical, externally produced tactile stimuli. In contrast, psychiatric patients with these symptoms did not show a decrease in their perceptual ratings for tactile stimuli produced by themselves as compared with those produced by the experimenter. It appeared that the presence of positive symptoms rather than a diagnosis of schizophrenia was responsible for the observed failure to perceive a difference between self and externally generated stimuli.

(314) Brebion *et al.*, (2000)	40 schizophrenia individuals 40 healthy controls.	24 items produced either verbally by the experimenter or participant or shown verbally. Participants were then read a recognition list including the produced target items mixed with distractors. Participants had to recognize the target items and to remember the source of their production.	Higher hallucination scores were associated with an increased tendency towards false recognition of non-produced items. Hallucinators were more prone than control subjects to misattribute to another source the items they had produced themselves. Hallucinators and delusional patients were more likely than other patients to report that spoken items had been presented as pictures.
(315) Foureret *et al.*, (2001)	19 schizophrenia: 10 *with Schneiderian symptoms* 9 *without* 19 matched controls.	Sensorimotor adjustment task.	Those patients that performed similarly to the control group (n=9) were aware of the manual correction and most of them presented with Schneiderian symptoms. The authors interpret this as implying that the experience of alien control observed in certain schizophrenic patients cannot therefore be directly related to an underlying cognitive deficit in the conscious monitoring of their own actions.
(316) Franck *et al.*, (2001)	6 schizophrenia patients with delusions of influence 18 schizophrenia patients without delusions of influence 29 controls.	Joystick action recognition task. The image of a virtual right hand holding a joystick was presented to the subjects through a mirror so that the image was superimposed on their real hand holding a real joystick. Subjects executed discrete movements in different directions. Angular biases and temporal delays were randomly introduced in some trials, such that the movement of the virtual hand departed from the movement executed by the subjects. After each trial, subjects were asked whether the movement they saw was their own.	Both groups made significantly more recognition errors in trials with temporal delays. The patient group with delusions made significantly more errors in trials with angular biases than both the other groups. Authors conclude that findings support the hypothesis that delusions of influence are associated with a quantifiable difficulty in correct self-attribution of actions.
(170) Stirling *et al.*, (2001)	40 schizophrenia individuals 36 controls.	Self-monitoring drawing task in which participants generated drawings of simple design and subsequently tried to identify their own drawings from drawings of the same design by other people in a recognition paradigm. General cognition and attention was also tested.	The patient group was significantly impaired on the self-monitoring task and this performance was related to both the severity and extent of positive symptoms. Authors concluded that these experimental findings provided support for the proposal that positive

			symptoms of schizophrenia arise as a result of deficiencies in self-monitoring.
(171) Turken *et al.*, (2003)	8 high functioning schizophrenia individuals 8 controls.	Assessed internal monitoring and attentional control (conflict resolution, set switching and preparatory attention) using same paradigm as Frith & Done (1989).	The patients exhibited no significant dysfunction of attentional control during task performance. However, their ability to correct errors without external feedback and by inference was significantly compromised.
(165) Knoblich *et al.*, (2004)	27 schizophrenia individuals, *split into those with either prominent paranoid hallucinatory or disorganisation syndrome, or those without* 23 controls.	Participants had to draw circles on an electronic pad connected to a PC; participants were instructed to continuously monitor the relationship between hand movements and the visual consequences and to detect changes in the mapping. This enabled self-monitoring and the ability to automatically correct movements to be assessed.	It was found that the symptomatic patients were selectively impaired in their ability to detect a mismatch between a self-generated movement and its consequences, but were not impaired in their ability to automatically compensate for the gain change. These results were interpreted as support for the claim that a failure of self-monitoring may underlie the core symptoms of schizophrenia.
(152) Henquet *et al.*, (2005)	15 schizophrenia individuals 15 controls.	Source monitoring task involved participants having to recall whether they had verbalized answers or merely thought about the answers. Other cognitive tests were undertaken.	Relative to the control, the schizophrenia group had significantly more difficulty with monitoring their own actions and showed a tendency towards misclassifying imagined thoughts as verbalized thoughts. Source-monitoring performance was related to selective attention, but not to other cognitive domains. No relationship was found between source monitoring and symptomatology.
(166) Krabbendam *et al.*, (2005)	37 with non-affective psychosis 41 first-degree relatives of patients with non-affective psychosis 40 high scoring individuals on CAPE 49 control participants scoring in the average range on positive	An action-investigation paradigm to investigate action monitoring in psychosis Subjects had to decide whether the movement they saw was similar to the movement they had made.	Patients made significantly more errors on trials with temporal delays, these were associated with delusional ideation and the strength of the association increased with increasing levels of delusional ideation. Number of errors on all trials was associated with psychosis risk with subjects with high levels of psychotic experiences and first-degree relatives having intermediate values between patients and controls. Authors concluded that findings provided support

	dimension of CAPE.		the idea that an impairment of self-monitoring is part of the liability to psychosis.
(317) Lidner *et al.*, (2005)	14 Schizophrenia individuals 2 matched control groups (n=14).	2 smooth-pursuit eye movement tasks, in which participants had to discriminate between retinal image motion resulting from either their own smooth-pursuit eye movements or from external motion sources.	A correlation was observed between the strength of delusions of influence and the ability of schizophrenia patients to cancel out such self-induced retinal information in motion perception. This correlation may reflect direct experimental evidence supporting the view that delusions of influence in schizophrenia might be due to a specific deficit in the perceptual compensation of the sensory consequences of one's own actions.

The 10 Gardner Hinting Tasks

Lisa is about to leave the house when her father's car pulls up in the driveway. When he enters she says to him: 'I really need to go shopping, but it's so far away and the rain is terrible.'

Question: What does Lisa really mean when she says this?

Extra information: Lisa goes on to say: 'It's only five minutes in the car.'

Question: What does Lisa want her father to do?

Alan is watching television, and his wife Jill sits down to join him. She says: 'I see you're watching the football. Isn't there anything else on at the moment?'

Question: What does Jill really mean when she says this?

Extra information: Jill then says to Alan: 'I thought there was a good play on the other channel'

Question: What does Jill want Alan to do?

Sarah is spending the morning with her next-door neighbour Caroline, having coffee. They are talking about Sarah's forthcoming holiday abroad, when Sarah says to Caroline: 'I'm worried that all my plants will be dead by the time I get back.'

Question: What does Sarah really mean when she says this?

Extra information: Sarh then says to Caroline: 'I have a spare key for the front door.'

Question: What does Caroline want Sarah to do?

Jack and his father are talking about the recent form of the local football team, which they both support. Jack says: 'You know United are playing at home to their big rivals this weekend. I'm sure it will be very exciting.'

Question: What does Jack really mean when he says this to his father?

Extra information: Jack goes on to say: 'I have never been to watch a football match.'

Question: What does Jack want his father to do?

Jim and his brother Richard are getting ready for work in the morning. Jim goes to the bathroom and finds that Richard is about to use the shower, and says to him: 'I've got an early start today and I'm running late.'

Question: What does Jim really mean when he says this to Richard?

Extra information: Jim goes on to say to Richard: 'It won't take me long to get ready.'

Question: What does Jim want Richard to do?

Harry and Chris work together in the same office. One day Harry says to Chris: 'I would really like an extra long lunch break today, as I have to go to the bank. Will you be going out for lunch today?'

Question: What does Harry really mean when he says this?

Extra information: Harry then says to Chris: 'Do you think our boss would mind if only one of us were here?'

Question: What does Harry want Chris to do?

On a weekday evening, Martin goes to see his friend Lucy at home. He is trying to persuade her to go out for a meal, but she says: 'I'm really busy writing a report tonight. I don't even have time to chat.'

Question: What does Lucy really mean when she says this?

Extra information: Lucy then says: 'really have to be getting on with my work, is there someone else you could ask.'

Question: What does Lucy want Martin to do?

Two children, Emma and Katie are playing, when Emma breaks an old statue belonging to Katie's mother. Emma says to Katie: 'If your Mum finds out it was me that broke it, I won't be allowed to come here anymore.'

Question: What does Emma really mean when she says this?

Extra information: Emma then says to Katie: 'She wouldn't punish you though.'

Question: What does Emma want Katie to do?

Tony and his girlfriend Alison are giving a dinner party at their new flat. They are going through the list of guests when Alison exclaims: 'Oh! It says here you've invited your ex-girlfriend. Is that right?'

Question: What does Alison really mean when she says this?

Extra information: Alison goes on to say to Tony: 'I don't get on with her very well.'

Question: What does Alison want Tony to do?

Simon is enjoying an evening out at the pub with his friend Gareth. Simon is about to buy some more drinks when Simon says: 'I have a very busy day tomorrow, and I need to be at my best.'

Question: What does Simon really mean when he says this?'

Extra information: Simon then says to Gareth: 'We have already had quite a lot to drink.'

Question: What does Simon want do?

The three Brüne cartoon picture sequences.

Cartoon 1: Wasp in the Bag

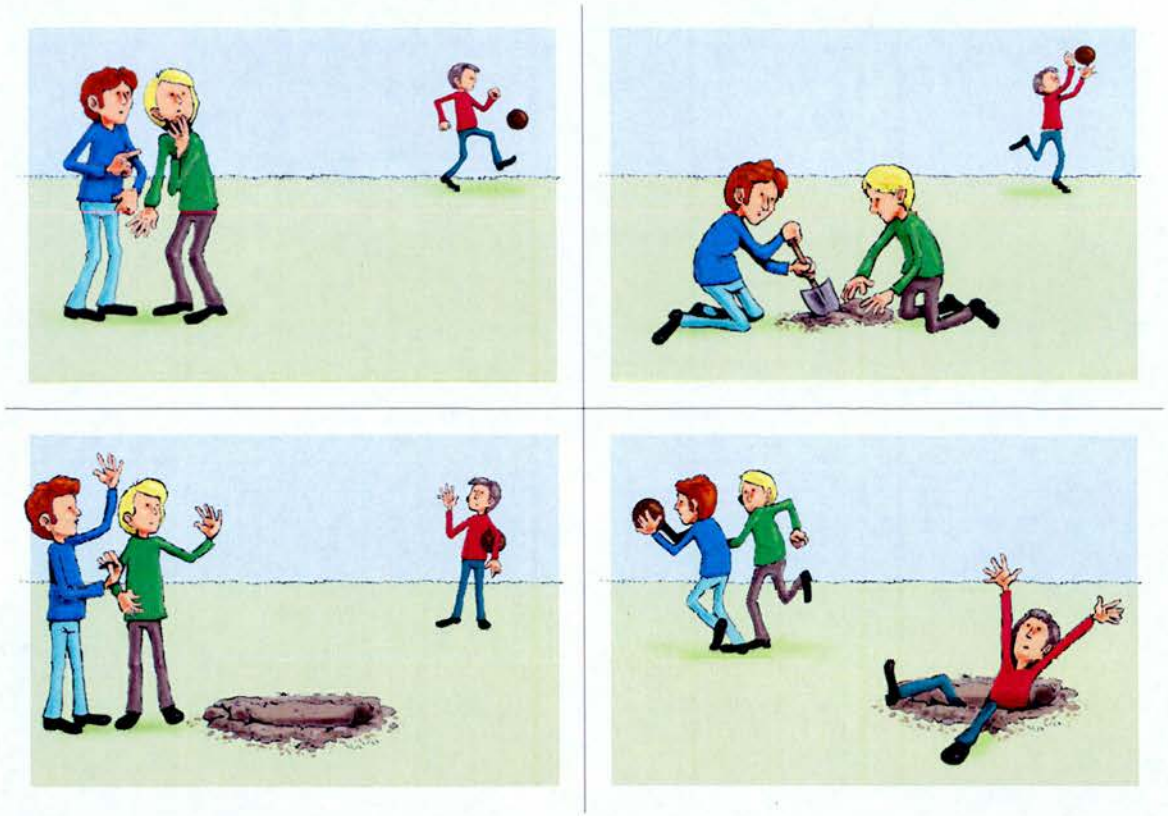
First order false belief question: What does the blond haired boy think is in the bag?

Reality question: What really is in the paper bag.

Second order false belief: What does the blond haired boy thinks his friend intends?

Tactical deception question: What does the brown haired boy intend?

Cartoon 2: Football



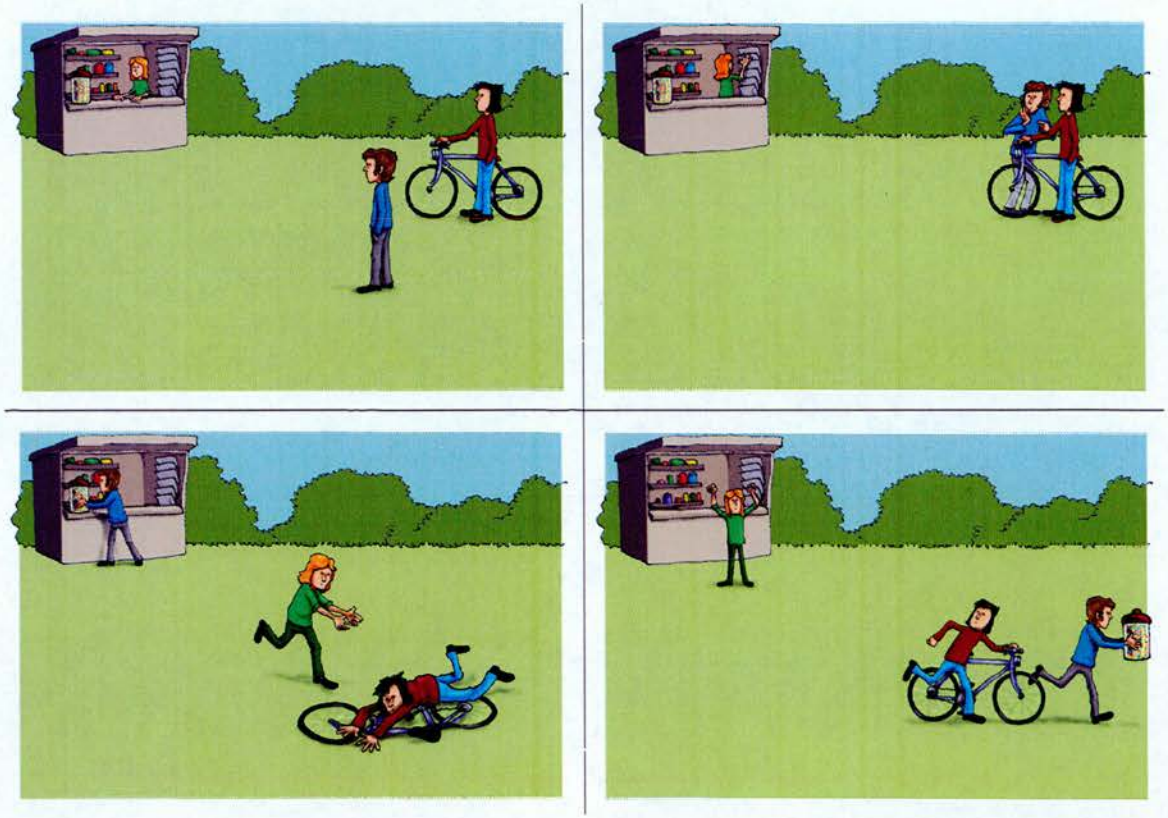
Second order false belief question: What does the boy in red believe the others intend?

Cheating question: What do the two others want the boy in red to believe what they intend?

Deception question: What do they really intend?

Cheating detection question: What does the boy in red now think the others have planned?

Cartoon 3: Sweets



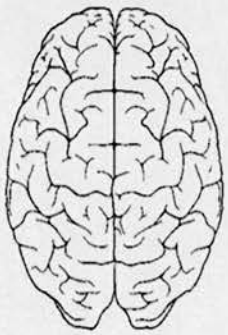
Cheating question: What do the boys in blue and red intend?

First Order false belief question: What does the shop girl believe happened?

Reciprocity question: What does the boy in red expect form the boy in blue?

Cheating detection: What does the shop girl now think the boys intended?

The three pictorial prompts used to signal what the corresponding block of 4 pictures were. A= ToM cartoons, B= Physical Cartoons, C= Jumbled Images.

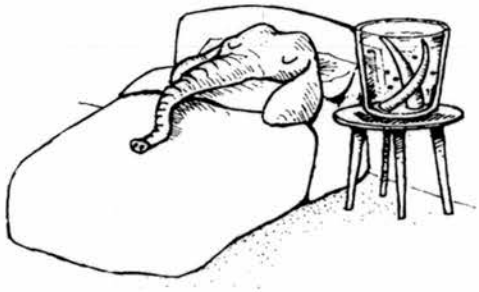


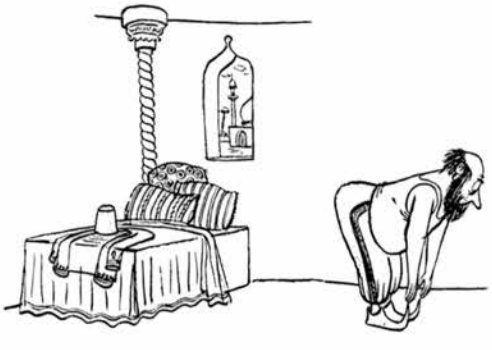
A

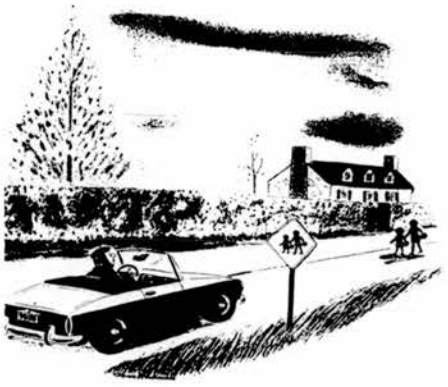
B

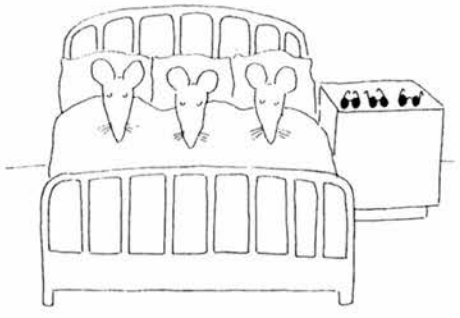
C

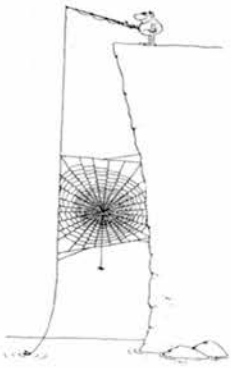
Physical Jokes:

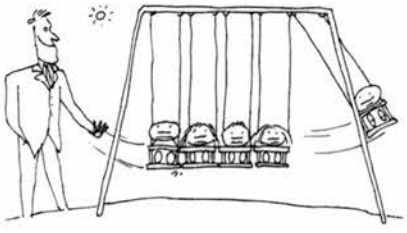


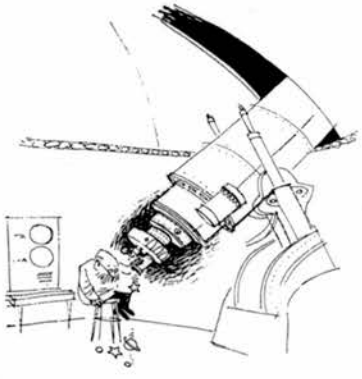


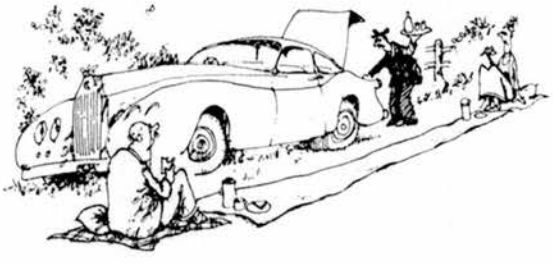


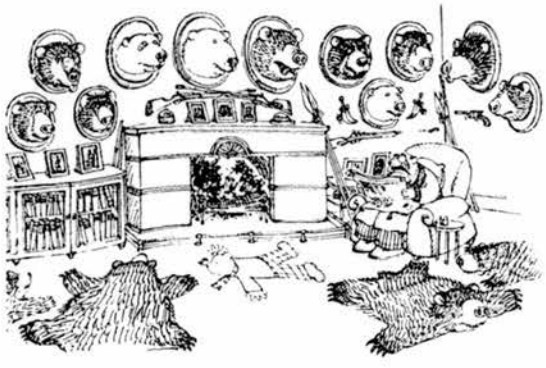




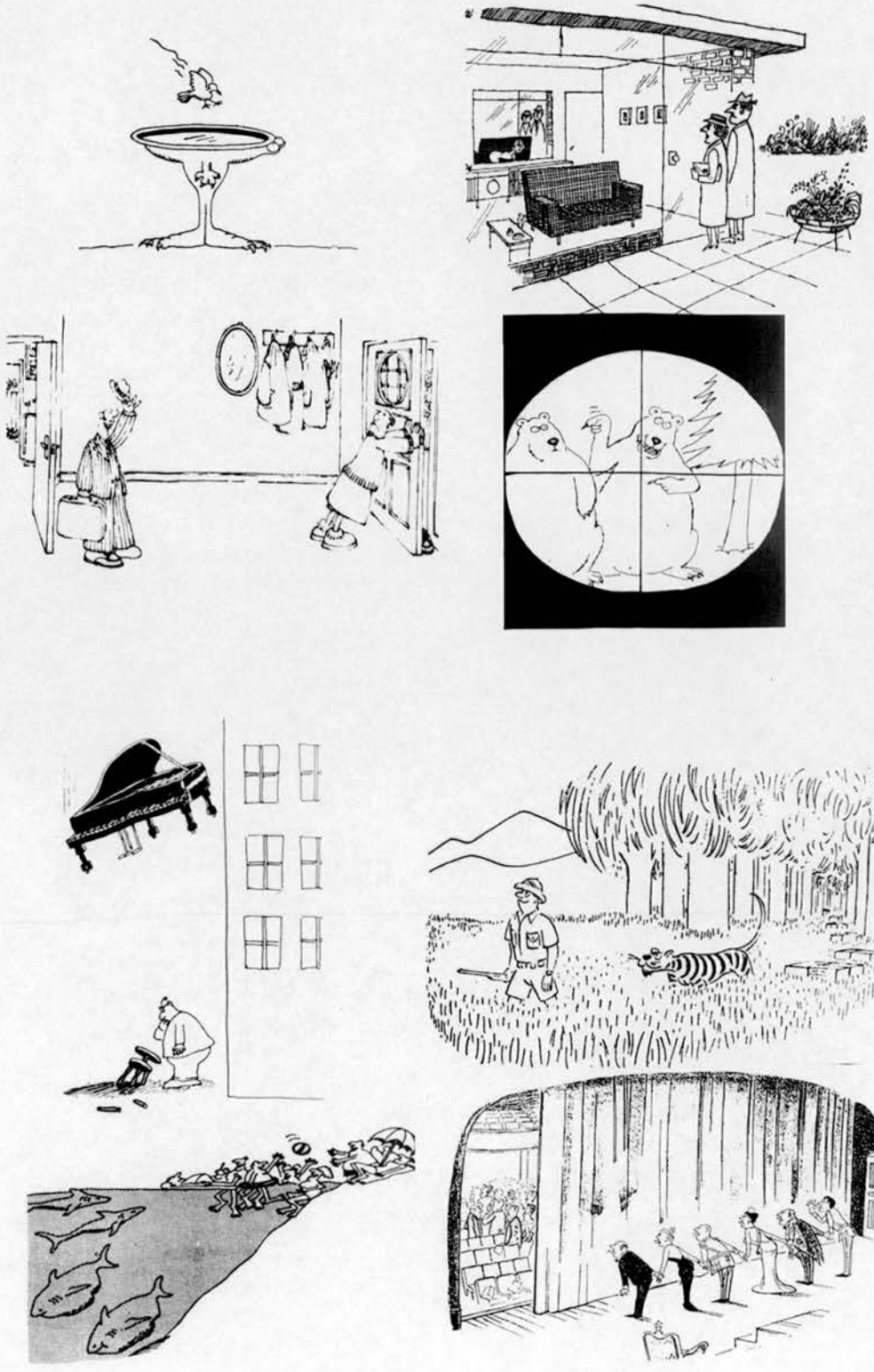


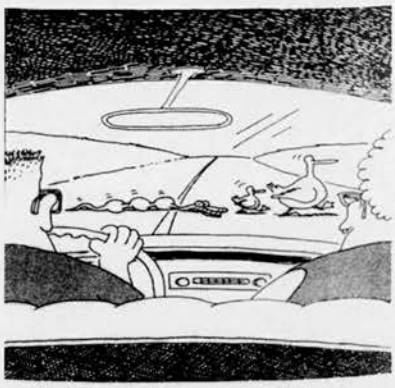


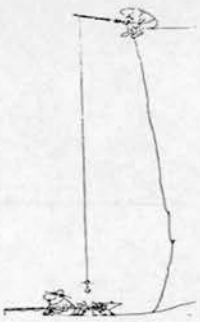


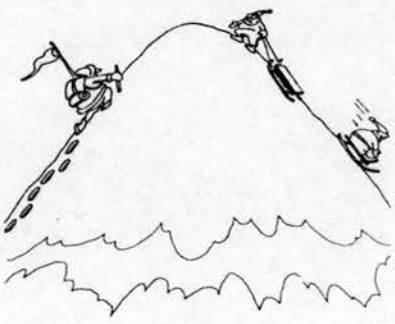


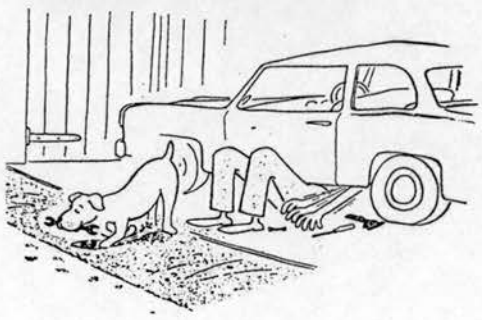
ToM Jokes:

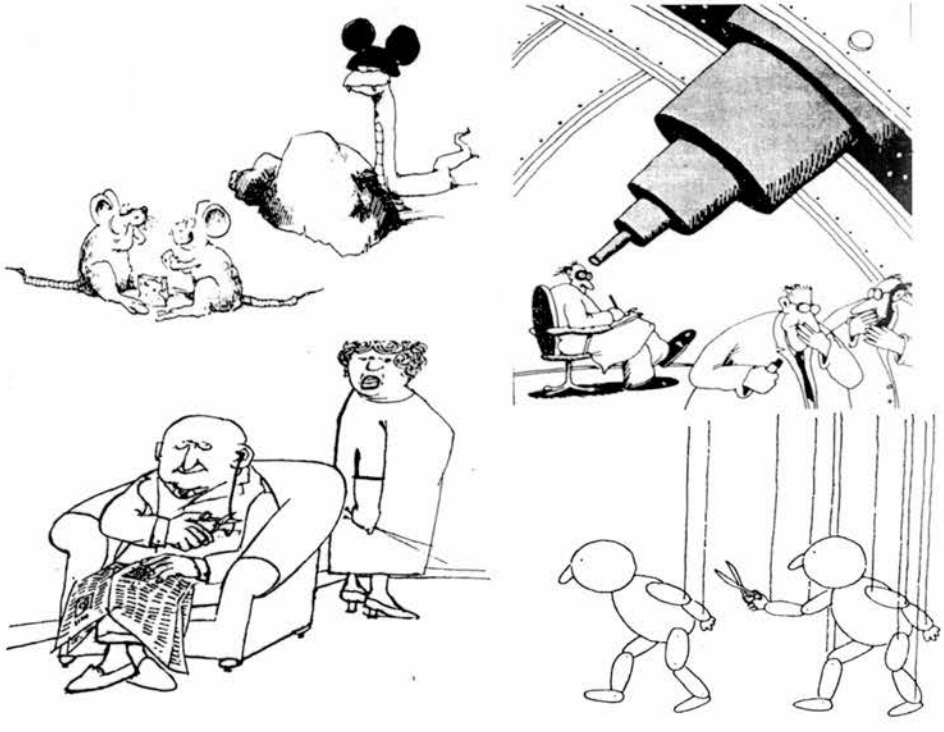




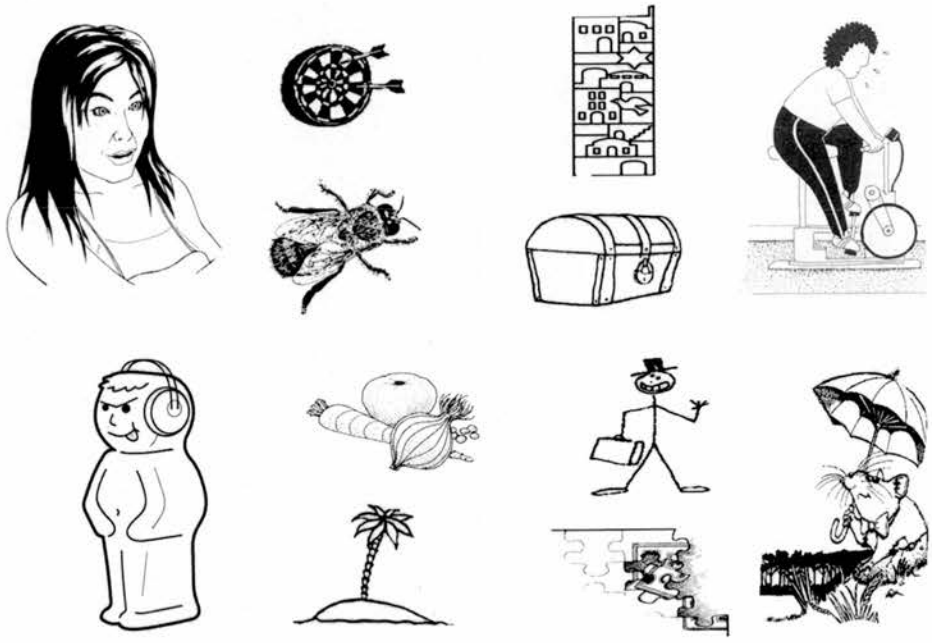


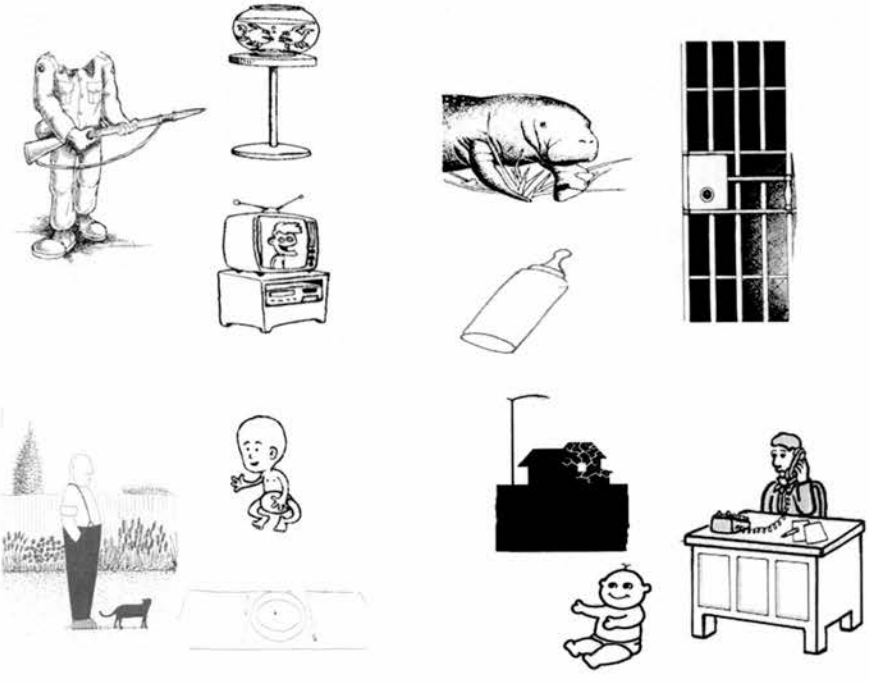


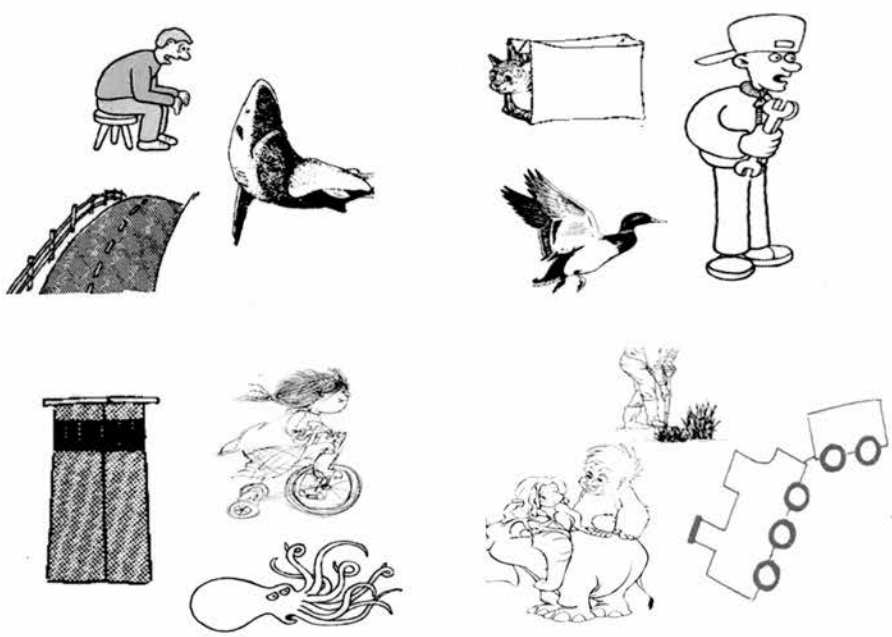




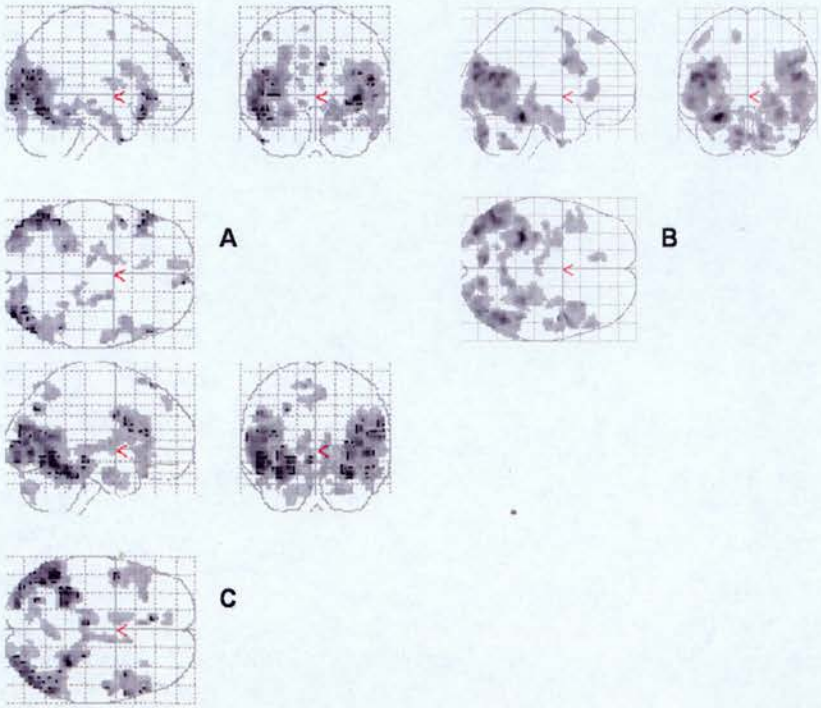
Jumbled Images:



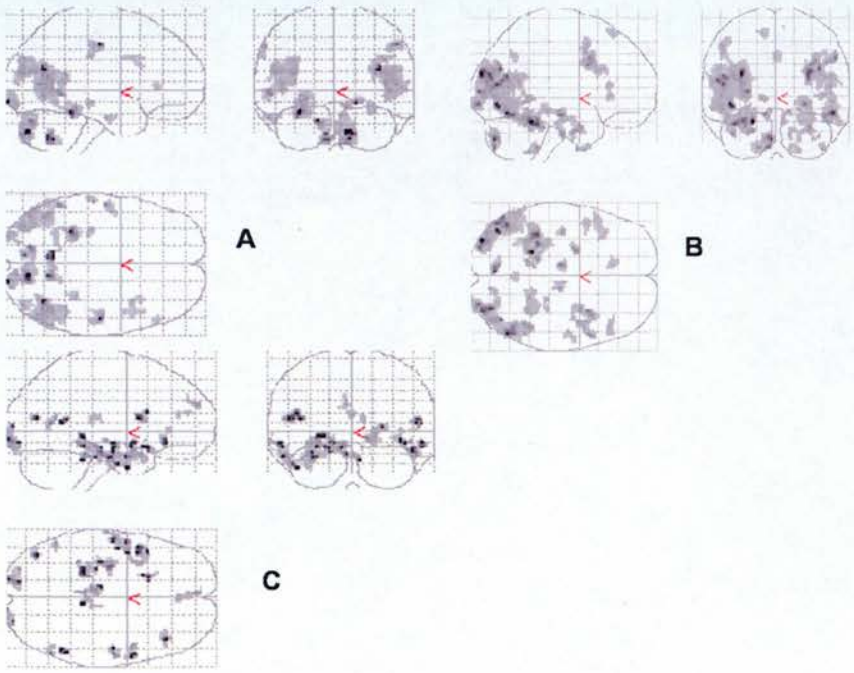




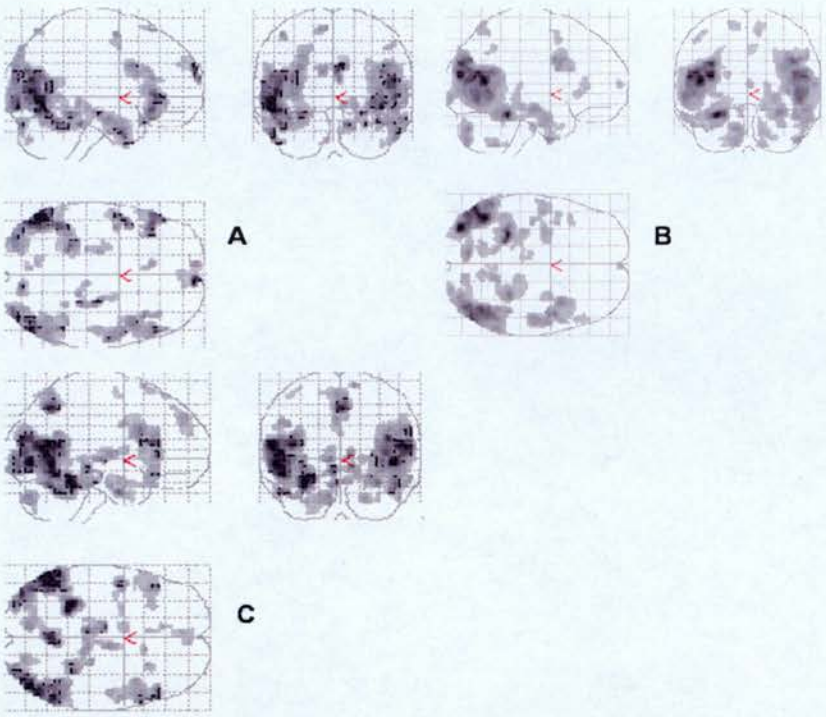
Additional MIPS:



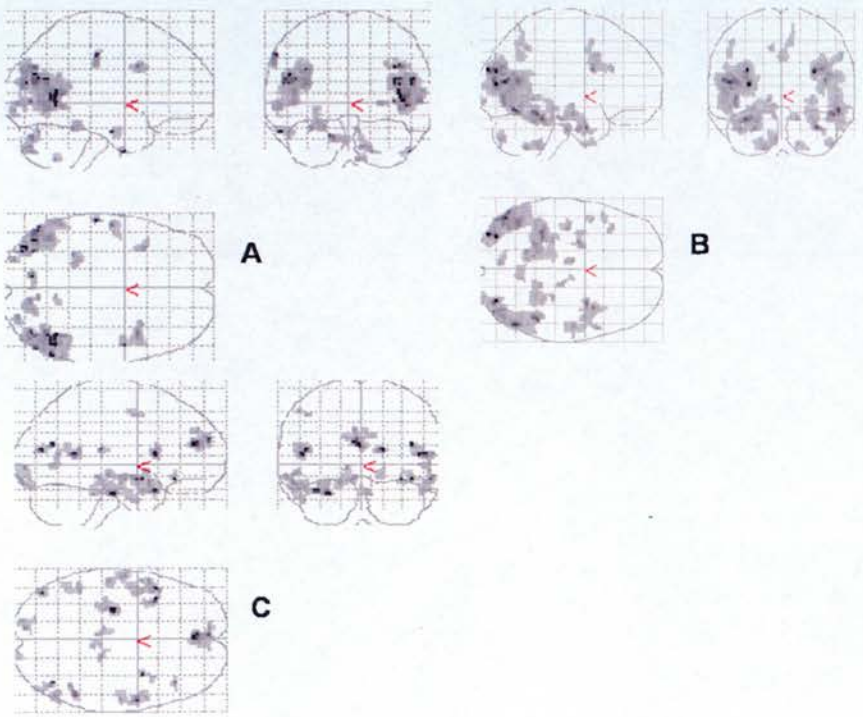
Phy vs Con contrast Maximum Intensity Projection image for Analysis 1 groups. Where A=HR-, B=HR+-, C=Controls.



Phy vs Con contrast Maximum Intensity Projection image for Analysis 2 groups. Where A=HR+Now, B=HR+Ever, C=HRill.



ToM vs Both Physical cartoons and Jumbled image contrast Maximum Intensity Projection image for Analysis 1 groups. Where A=HR-, B=HR+-, C=Controls.



ToM vs Both Physical cartoons and Jumbled image contrast Maximum Intensity Projection image for Analysis 2 groups. Where A=HR+Now, B=HR+Ever, C=HRill.

Table 3 *Analyses 1 & 2 within group significant activations for ToM vs Physical and Control images.*

Condition & Group	*P*	*Extent*	*Z*	*Peak height (x,y,z)*	*Region*
ToM vs Phy&Con					
HR-	P<0.0001	3332	4.86	-53 -64 -1	Left Inferior Temporal Gyrus BA37
	P<0.0001	2450	4.45	50 -71 18	Right Middle Temporal Gyrus BA39 (TPJ)
	P<0.0001	753	4.29	51 31 -2	Right Inferior Frontal Gyrus BA47
	P=0.001	522	4.07	-46 27 -11	Left Inferior Frontal Gyrus BA47
	P=0.001	461	461	53 5 -24	Right Middle Temporal Gyrus BA21
HR+	P<0.0001	3557	5.77	-34 -81 21	Left BA19 Occipital Lobe
	P<0.0001	600	5.50	-28 -40 -15	Left Fusiform Gyrus BA36
	P<0.0001	4033	5.03	44 -61 20	Right STS/STG BA39
	P<0.0001	604	4.47	48 5 29	Right Posterior Frontal lobe BA6
	P<0.0001	570	4.41	30 -38 -13	Right Fusiform Gyrus BA36
	P=0.034	275	4.29	-10 -75 -25	Left Cerebellum
	P=0.002	457	4.18	48 -2 -37	Right Inferior Temporal Gyrus BA20
	P=0.022	300	3.69	-50 -9 -25	Left Inferior Temporal Gyrus BA20
Controls	P<0.0001	3270	5.01	46 -76 2	Right Middle Occipital Gyrus BA19
	P<0.0001	3683	4.97	-30 -43 -15	Left Cerebellum
	P=0.001	521	4.56	0 -58 47	Left Precuneus BA7
	P<0.0001	828	4.32	57 24 14	Right Inferior Frontal Gyrus BA45
	P=0.018	317	4.07	-6 -29 -5	Left Brainstem
	P=0.003	425	4.40	-48 25 -13	Left Inferior Frontal Gyrus BA47
	P=0.035	278	3.93	32 -40 -22	Right Cerebellum
	P=0.041	269	3.62	-10 -78 -34	Left Cerebellum
HR+Now	P<0.0001	1472	4.54	42 -68 35*	Right Superior Parietal Lobule BA19
	P<0.0001	1163	3.91	-52 -71 22	Left Gyrus Angulairs BA39
	P=0.031	101	3.56	10 -77 -28	Right Cerebellum
HR+Ever	P<0.0001	2697	5.10	-30 -79 4	Left Occipital Lobe BA18
	P<0.0001	1624	4.88	30 -78 24	Right Occipital Lobe BA19
	P=0.013	124	4.25	36 19 21*	Right Inferior Frontal Gyrus BA45
	P=0.048	99	4.01	-26 -7 -27	Left Parahippocampul Gyrus BA36
	P=0.003	157	3.98	-16 -54 -39	Left Cerebellum
	P=0.002	168	3.90	51 -10 -15	Right Middle Temporal Gyrus BA21
	P=0.009	132	3.86	-12 -47 -1	Left Gyrus Lingualis BA30
	P=0.003	157	3.62	30 -40 -17	Right Fusifrom Gyrus BA37
	P=0.030	108	3.45	-40 26 21	Left Middle Frontal Gyrus BA45/46
HRill	P<0.0001	95	3.56	-2 45 16	Left Medial Frontal Gyrus BA9
	P<0.0001	69	3.47	-28 -20 -21	Left Gyri Hippocampi BA36
	P<0.0001	101	3.46	-36 13 -21	Left Superior Temporal Gyrus (Temporal Pole) BA38
	P<0.0001	73	3.11	55 0 -10	Right Middle Temporal Gyrus BA21 (STS)